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OFFICE OF HUMAN GENOME RESEARCH

Administrative Plan

In recognition of the high priority placed on mapping and sequencing the human genome, and the overarching planning and resource demands of a systematic targeted effort, it is proposed that an Office of Human Genome Research be established within the Office of the Director, NIH. The function of the Office will be to provide coordination, integration, review of progress, and planning in genomic analysis research. Research goals and long-range plans will be formulated with the guidance of the NIH Program Advisory Committee on the Human Genome and the NIH Working Group on the Human Genome *Coordinating Committee*

Coordination Function

Given the current broad involvement in research related to the characterization of complex genomes, the essential coordination and integration function of the Office will span four areas:

- o Overall intra-agency NIH coordination;
- o Interagency coordination between NIH and other Federal agencies (DOE and NSF), and other research-funding organizations;
- o Collaboration with industry and academia; and
- o International cooperation.

The Office of Human Genome Research is envisioned as a new entity with a mandate to develop proposals for analysis of complex genomes. This strategy is not intended to supersede ongoing efforts within other NIH components, but to integrate those efforts into a cohesive plan. One goal will be to maximize the efficiency of information exchange regarding new mapping data, improved techniques for storage and handling of biological material, and enhanced data processing and analysis. Therefore, centralized coordination will rely heavily on effective interactions with BID programs, as well as with other research funding organizations and the academic research community.

The NIH Program Advisory Committee on the Human Genome

The NIH Program Advisory Committee on the Human Genome will be comprised of non-Federal employees with demonstrated expertise in the scientific disciplines related to genomic analysis. The Committee will advise the NIH on all aspects of genomic analysis. The Committee will identify opportunities to further advance characterization of the genetic material of many organisms. The Committee will also recommend initiatives that should be undertaken to promote the development of new technologies that will lead to a deeper understanding of molecular biology. The Committee will also advise on research directions and identify areas of research requiring additional effort. The Committee will propose administrative solutions to the resource and training needs of the research community, specific to genomic analysis.

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Of necessity, the membership of the NIH Program Advisory Committee on the Human Genome will represent a number of diverse research disciplines including, but not limited to, molecular genetics, physical chemistry, bioengineering, mathematics, and computer science.

The Office of Human Genome Research

The Office of Human Genome Research will serve as a focus within NIH and with other components of Public Health Service, reviewing policy questions, and coordinating plans for future research efforts. The Office will play an important role in exchanging information on the scientific activities in the Intramural Research Program. The Office will provide an internal framework for the review and consideration of a number of issues requiring the viewpoint of the biomedical research community.

Leadership for this initiative will be provided by the NIH Associate Director for Human Genome Research. This position will be held by a distinguished scientist who will be expected to remain current in his/her discipline. One means for recruiting such an individual would be to classify the position as part-time, offering the opportunity to maintain an ongoing research program. The Director of the Office of Human Genome Research will be responsible for day-to-day administrative operations in accordance with the guidance of the Associate Director.

The Office of Human Genome Research will develop a plan for a centralized, systematic, targeted effort to create detailed maps of the genomes of several organisms. The precise order and choice of goals would be determined with the advice of the Program Advisory Committee, but examples might include yeast, Drosophila, Caenorhabditis elegans, mouse, and human genomes.

The Office of Human Genome Research will not have a research budget to fund new initiatives. These initiatives will be supported by the BIDs and will pay particular attention to interdisciplinary projects that may not have a traditional locus in one BID. In addition, the coordination function of the Office will facilitate multiple Institute support for suitable proposals.

All grants and contracts funded as part of the genome program will be approved in accordance with traditional NIH peer review procedures.

MEMORANDUM OF UNDERSTANDING
BETWEEN THE
UNITED STATES DEPARTMENT OF ENERGY
AND THE
NATIONAL INSTITUTES OF HEALTH

TO COORDINATE RESEARCH AND TECHNICAL ACTIVITIES
RELATED TO THE HUMAN GENOME

I. Introduction

The National Institutes of Health (NIH), Department of Health and Human Services, and the United States Department of Energy (DOE) agree to foster interagency cooperation that will enhance the human genome research capabilities of both agencies.

DOE and NIH are the Federal Agencies primarily responsible for supporting research relating to the human genome. There has been considerable discussion in the scientific community over the past two years about the need for a coordinated long-term project to map and sequence the human genome. While NIH and DOE have informally coordinated such research efforts, the increasing complexity and scope of the project require a more formal mechanism. The purpose of this Memorandum of Understanding (MOU) is to provide for the formal coordination of the activities of DOE and NIH, and to provide for interfaces with relevant activities both within and outside the United States. The MOU also provides a mechanism by which NIH and DOE can jointly obtain outside advice regarding the human genome project.

II. Definition

For the purposes of this MOU, human genome research encompasses efforts to develop and apply technologies for the large-scale mapping, sequencing and analysis of the human genome. It includes the development of shared centralized facilities such as repositories for cloned DNA fragments, databases, and data centers to collect and distribute the large amounts of information generated on the project.

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III. Goals

The goals of the project include: completion of a high-resolution genetic map of the human genome; completion of a series of complementary physical maps of increasing resolution; acquisition of a collection of ordered DNA clones encompassing the entire genome; determination of the complete nucleotide sequence of a reference genome; location of all the genes; and development of the tools to use the above information for a variety of biological and medical applications. Parallel studies in model organisms will be required in order to achieve a full understanding of the human genome.

IV. Management and Program Guidelines

- A. Establishment of a joint advisory subcommittee chosen from the members of the DOE Health and Environmental Research Advisory Committee and the NIH Program Advisory Committee on the Human Genome.

The joint subcommittee will receive charges jointly prepared by NIH and DOE and communicated to their appropriate parent advisory committees. The joint subcommittee shall be co-chaired by representatives from the DOE and NIH committees. The joint subcommittee shall meet quarterly in order to advise and review the relevant activities of the two agencies. Subcommittee reports will be delivered through the two parent advisory committees to appropriate senior officials of NIH and DOE.

- B. Establishment of an Interagency Working Group (IAWG) on genome research between DOE and NIH. The IAWG will be co-chaired by NIH and DOE and will meet at least on a quarterly basis to explore the need for and the feasibility of initiating a variety of cooperative and complementary programs and projects in order to advance knowledge in human genome research. The IAWG will also provide oversight of activities carried out under this MOU. In addition to the chairpersons, the IAWG will consist of an equal number of full members from DOE and NIH. Additional ad hoc members may be added for temporary assignments by either agency with prior concurrence of the chairpersons.

- C. Continued coordination with other Federal agencies, with outside scientific groups, both national and international, and with private organizations involved in the genome project.

- D. Continued joint participation and sponsorship of meetings and workshops for the purposes of planning and review of technical progress including an annual symposium to review progress in the science, to identify areas of need, and to address general policy questions.
- E. Development of synchronous calendars for the agencies' research award cycles.
- F. Concurrent funding and management of selected programs in human genome research that require utilization of unique NIH or DOE facilities.
- G. Maintenance of regularly scheduled joint program staff meetings to exchange program information and plans.
- H. Promotion of the sharing of technological advances and relevant biological materials (probes, cell lines, etc.) among investigators supported by both agencies. Assurance that relevant data are rapidly placed in appropriate databases and that relevant biological materials are rapidly placed in appropriate repositories.
- I. Promotion of coordination and exchange of data with other countries.
- J. Advance sharing of public policy statements relevant to human genome research.

V. Administration

- A. Public Information Coordination: Subject to the Freedom of Information Act (5 U.S.C. 552), decisions on disclosure of information to the public regarding projects and programs implemented under the Memorandum of Understanding will be made following consultation between DOE and NIH representatives.
- B. Intellectual Property: Specific provisions concerning the disposition of rights in intellectual property will be included in any interagency agreement under this Memorandum of Understanding.
- C. Amendment and Termination: This Memorandum of Understanding may be modified or amended by written agreement between NIH and DOE and terminated by mutual agreement of DOE and NIH or by either party upon 90-day written notice to the other.

D. Effective Date: This Memorandum of Understanding is effective when signed by both parties.

James B. Wyngaarden
James B. Wyngaarden
Director
National Institutes of Health

Sept 30, 1988
Date

Robert O. Hunter, Jr.
Robert O. Hunter, Jr.
Director
Office of Energy Research
U. S. Department of Energy

October 7, 1988
Date



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

CHARTER

PROGRAM ADVISORY COMMITTEE ON THE HUMAN GENOME

Purpose

The Program Advisory Committee on the Human Genome will advise the NIH on all aspects of research in the area of genomic analysis. The Committee will identify opportunities to advance the ability of scientists to analyze the composition and organization of the genetic material of a number of organisms, with the goal of applying this information to the analysis of the human genome. The Committee will recommend initiatives that will promote the development of new technologies that will facilitate the acquisition, interpretation, analysis, and distribution of genetic and physical mapping information and deoxyribonucleic acid (DNA) sequence data. The Committee also will advise on research directions and identify areas of research requiring additional effort. The Committee will address the resource and training needs of the research community, as they pertain to genomic analysis.

Authority

42 U.S.C. 217a (Section 222 of Public Health Service Act as amended). This Committee is governed by provisions of P.L. 92-463, as amended (5 U.S.C. Appendix 2), which sets forth standards for the formation and use of advisory committees.

Function

The Program Advisory Committee on the Human Genome shall advise the Secretary; the Assistant Secretary for Health; the Director, National Institutes of Health; the Associate Director for Human Genome Research, National Institutes of Health; and the NIH Working Group on the Human Genome on long- and short-term planning to meet research needs for genomic analysis. Specifically, the Committee shall identify opportunities to further research on information and database technology and the methodology of genomic analysis and the characterization of the genomes of a variety of organisms, with the goal of applying this knowledge to the analysis of the human genome and ultimately to the prevention, diagnosis, and treatment of human disorders; recommend areas in which research should be stimulated; and suggest conferences, workshops, or other activities that the NIH should support to further the development of this research area.

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Structure

The Program Advisory Committee on the Human Genome shall consist of 12 members selected by the Secretary, who shall be authorities knowledgeable in the fields of basic genetics, medical genetics, molecular biology, biochemistry, physical chemistry, information science, and engineering. The chair shall be selected by the Secretary from the membership and shall serve for at least one year and may be reappointed.

Members are invited to serve for overlapping four year terms, except that a member may serve after the expiration of the member's term until a successor has taken office. Terms of more than two years are contingent upon the renewal of the charter of the Committee by appropriate action prior to its expiration.

Management and support services shall be provided by the Office of the Associate Director for Human Genome Research, Office of the Director, NIH.

Meetings

Meetings shall be held at least twice a year at the call of the Chair with the advance approval of a Government official who will also approve the agenda. A Government official shall be present at all meetings. A quorum for the conduct of full committee business shall be seven.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of the proceedings kept as required by applicable laws and departmental regulations.

Compensation

Members shall be paid at the rate of \$200 per day for time spent at meetings, plus per diem and travel expenses as authorized by Section 5703, Title 5, United States Code, for persons in the Government service employed intermittently. Members who are officers or employees of the United States shall not receive compensation for service on the Committee.

Annual Cost Estimate

Estimated annual cost for operating the Committee, including compensation and travel expenses for members but excluding staff support, is \$65,944. The estimated annual staff years of support is .45 at an estimated cost of \$18,234.

Reports

An annual report shall be submitted to the Secretary; the Assistant Secretary for Health; and the Director, National Institutes of Health, which shall contain, as a minimum, the Committee's functions, a list of members and their business addresses, the dates and places of meetings, and a summary of the Committee's activities and recommendations during the year. A copy of the report shall be provided to the Department Committee Management Officer.

Termination Date

Unless renewed by appropriate action prior to its expiration, the Program Advisory Committee on the Human Genome shall terminate two years from the date of establishment.

APPROVED:

JUL 21 1988

Date

Otis R. Bowen M.D.

Otis R. Bowen, M.D.
Secretary

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PROGRAM ADVISORY COMMITTEE
ON THE HUMAN GENOME

FIRST MEETING

January 3 and 4, 1989

Building 31, C Wing, Conference Room 6
National Institutes of Health
Bethesda, MD

MINUTES

The first meeting of the Program Advisory Committee on the Human Genome took place on January 3 and 4, 1989, in Bethesda, MD. The following Committee members attended:

Norton D. Zinder, Ph.D., Chairman
Elke Jordan, Ph.D., Executive Secretary
Bruce M. Alberts, Ph.D.
David Botstein, Ph.D.
Jaime G. Carbonell, Ph.D.
Joseph L. Goldstein, M.D.
Leroy E. Hood, Ph.D.
Victor A. McKusick, M.D.
Maynard V. Olson, Ph.D.
Mark L. Pearson, Ph.D.
Cecil B. Pickett, Ph.D.
Phillip A. Sharp, Ph.D.
Nancy S. Wexler, Ph.D.

The following liaison members also attended:

George F. Cahill, Jr., M.D.
C. Thomas Caskey, M.D., F.A.C.P.
Mary E. Clutter, Ph.D.
Robert M. Faust, Ph.D.
Benjamin J. Barnhardt, Ph.D.

Drs. Goldstein and Clutter were unable to attend the second day of the meeting. The Committee roster and lists of speakers and others who attended are attached to these minutes.

DAY 1

Dr. James B. Wyngaarden, Director of the National Institutes of Health (NIH), began the meeting with an overview of the history of NIH's role in genetics research. He noted that NIH has invested in this type of research for several decades, by sponsoring intramural programs as well as by providing resources to the extramural scientific world. Dr. Wyngaarden reported that, in FY 1988, Congress awarded NIH the sum of \$17.2 million to conduct research on the mapping and sequencing of the human genome. Following this appropriation, NIH

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held a major retreat in Reston, VA, to discuss the project and determine the role NIH would play. Dr. Wyngaarden summarized the meeting's accomplishments, one of which was the creation of the Office of Human Genome Research within the Office of the Director, NIH. In addition, the meeting defined four sub-areas of the human genome project: improvement of information management, improvement of methodology, mapping of the genome, and determination of the nucleotide sequence.

Next, Dr. Wyngaarden delivered the charge to the Program Advisory Committee. He stated that the Committee is empowered to advise NIH on all aspects of the human genome project, including new technologies, new directions, training needs, etc. In addition, the Committee will be expected to assist in preparing a plan for the human genome project, which is due to be submitted to Congress in early 1990. In discussing the definition and boundaries of the project, Dr. Wyngaarden noted that virtually all Institutes of the NIH are involved in research that interacts with this program. He stated that the Office of Human Genome Research does not wish to usurp projects that have been undertaken by individual Institutes; rather, it seeks to coordinate efforts into a cohesive plan and to determine what can be done differently.

Dr. Norton D. Zinder, of The Rockefeller University, began his remarks by noting that this meeting marked the formal beginning of the NIH human genome project. He stated that obtaining the sequence of the human genome is "a priceless endeavor" and that the project will be endless: Once the sequencing has been completed, the information must be used, and the applications are almost limitless.

Dr. Zinder proceeded to set the dates for future Committee meetings. The next meeting will be held on June 19-20, 1989, and the following meeting will take place on December 4-5, 1989. The latter meeting will include discussion of the report to be submitted to Congress by March 1990.

Dr. James D. Watson, Associate Director for Human Genome Research, NIH, discussed the background and goals of the human genome project. He stated his intention to complete the project "as fast as possible within a reasonable cost." He estimated that approximately 15 to 20 years would be required to complete the entire project but that important results are likely to be produced within the next 5 years.

Dr. Watson discussed coordination of projects under the program. He felt that small laboratories consisting of 5 to 10 scientists working on special projects will probably not be sufficient to achieve program goals. Larger groups--even centers--may be necessary. Decisions about which laboratories should be encouraged to grow larger will have to be made, and this is an area in which the Office of Human Genome Research and the Program Advisory Committee must become involved.

Dr. Watson stated his belief that the human genome project must be run by the scientific community. He urged the Committee members to travel and get to know the laboratories that will be doing the work rather than simply reading their proposals. Dr. Watson also emphasized that the Advisory Committee was not convened to ratify decisions that had already been made; rather, the Committee will make decisions that will influence the direction of the program at NIH.

Dr. Elke Jordan, Director of the Office of Human Genome Research, NIH, described the function of the Office and discussed its interaction with other groups. She announced the creation of the NIH Coordinating Committee on the Human Genome, which consists of representatives from the Institutes of NIH that are involved in genome-related research (i.e., almost all the Institutes). The Coordinating Committee will facilitate communication between the Institutes and the Office of Human Genome Research. In addition, Dr. Jordan discussed the collaboration between NIH and the U.S. Department of Energy (DOE), which has been established through a Memorandum of Understanding (MOU) between the two agencies. The Health and Environmental Research Advisory Committee (HERAC) of DOE and the Program Advisory Committee of NIH will form subcommittees that will meet jointly to fulfill the requirements of the MOU.

Dr. Jordan also stated that the Office of Human Genome Research will interact with the Human Genome Organization (HUGO) to facilitate coordination of genome research internationally. She noted that representatives from other countries involved in this type of research may be invited to future Committee meetings to provide updates on their activities.

Following this presentation, Dr. Ruth Kirschstein summarized ongoing research on the human genome that is sponsored by the National Institute of General Medical Sciences (NIGMS). She described two NIH-wide program announcements, issued in May 1987, entitled "New Approaches to the Analysis of Complex Genomes" and "Computer-Based Representation and Analysis of Molecular Biology Data." Initially, solicitations sought applications involving development of methods to fragment, purify, and clone large segments of DNA; to develop ordered sets of such fragments; to explore better ways of sequencing the fragments in order to expand the genetic and physical maps of the human and other genomes; and to conduct computational analyses of data. Dr. Kirschstein also discussed the Request for Applications (RFA), published in October 1987, for research initiatives involving the human genome and those of model organisms (yeast, *Drosophila*, the mouse, and *Caenorhabditis*). She noted that two special study sections had been created to review the applications submitted by the scientific community.

Dr. Kirschstein reported that 63 grants were funded in FY 1988. The largest number of these grants involved technology development and instrumentation, and 23 were specifically related to the human genome. Dr. Kirschstein estimated that approximately \$12 million will be available in FY 1989 for new research and that approximately 30 to 40 additional grants will be funded.

Dr. Irene Eckstrand of NIGMS described the Institute's plans to sponsor meetings and workshops, including the Human Gene Mapping Workshop, which is to be held June 10-17, 1989, in New Haven, CT. She also reported that NIGMS, DOE, and Howard Hughes Medical Institute will cosponsor a series of meetings on data management for physical mapping information. These meetings will deal with nomenclature, software, and data base management.

Dr. Eckstrand stated that NIGMS also plans to facilitate collaborations among investigators working on similar projects in order to improve communication and to design networks for data transfer and analysis. With these goals in mind, NIGMS will sponsor a meeting in March 1989 of approximately 25 investigators who are working on chromosome 11. In the fall of 1989, a meeting will be held to address strategies and technologies for DNA sequence determination.

During discussion of these presentations, Dr. Kirschstein stated that NIGMS had used the FY 1988 and FY 1989 funds primarily for research projects and had not allocated funds directly for training, although research grants supported training indirectly. Dr. Kirschstein also commented that NIGMS was able to provide funds for equipment needs in the scientific community but that authority for construction was not available.

Dr. Donald A.B. Lindberg provided background on the National Library of Medicine (NLM) and discussed NLM's plans to augment existing resources by developing factual data bases, particularly for microbiology and biotechnology. He described a new information model whereby data reside where they have been created, and users access the data through networks. He noted that NLM plans an active role in managing such networks. Dr. Lindberg also stated that NLM has recently funded projects on information processing and will continue to support this type of research in 1989. In addition, he mentioned that NLM has funded training grants in medical informatics for the last 20 years.

Dr. Lindberg reported that the National Center for Biotechnology Information has been established at NLM and is funded at \$8 million per year. He stated that the Committee's input on optimal ways to use the Center will be sought.

Dr. Daniel R. Masys presented further detail on NLM's biotechnology information program, which focuses on problems specific to automated information systems, e.g., nonstandard vocabularies, structures, and searching methods. He stated that the National Center for Biotechnology Information has been charged with the following tasks:

- To design, develop, implement, and manage automated information systems for human molecular biology, biochemistry, and genetics;
- To perform research in advanced methods of computer-based information processing capable of representing and analyzing the vast number of biologically important molecules and compounds;
- To enable use of the systems and methods developed; and
- To coordinate international gathering of biotechnology information.

Dr. Masys summarized NLM-supported projects that have been ongoing for the last several years in the following areas:

- Development of new data bases and enhancement of existing ones, e.g., through the design of linkage schemes;
- Improvement of information retrieval and analysis; and
- Communication, including sponsorship of meetings and workshops on computational biology, e.g., the Macromolecules, Genes, and Computers Workshop to be held in the summer of 1989.

During discussion of issues surrounding the design of information systems, several participants cautioned against overstandardization in the organization of data from areas of research that are highly experimental. Dr. Masys stated

that input from the Committee would be important in making decisions about the types of data bases that should be supported (e.g., Are separate data bases for nucleic acids and proteins necessary, or would it be advantageous to combine them?). Dr. Lindberg noted that outreach is an area of major concern at NLM, and ways of educating the scientific community about available resources are being explored.

Dr. James C. Cassatt described the NIGMS-funded GenBank, a data base that contains not only sequence information but also bibliographic data and biological information pertaining to the sequences. GenBank currently contains more than 22,000 entries comprising approximately 24,000,000 base pairs, and data are available online as well as on magnetic tapes, floppy disks, and CD-ROM. GenBank also collaborates with other nucleic acid sequence data bases--the European Molecular Biology Laboratory (EMBL) in Heidelberg and the DNA Data Bank of Japan.

Dr. Cassatt stated that future challenges include insuring that GenBank data are complete and up to date. He emphasized the importance of timely data entry and reported that a user-friendly program to facilitate data entry will be available to the research community in 2 months. In addition, journals that publish sequence information will be asked to require authors to enter their data into GenBank upon acceptance of their manuscripts.

During the discussion period, several participants stressed that the Committee should work on ways to encourage investigators to enter their data into appropriate data bases quickly.

Dr. Delbert H. Dayton described the Repository of Human DNA Probes and Libraries, which is funded jointly by the National Institute of Child Health and Human Development and the Division of Research Resources (DRR). The Repository, an international facility that has served 2,667 users, provides for the reliable exchange of cloned human DNA and the distribution of chromosome-specific libraries. The American Type Culture Collection (ATCC), which operates the Repository, accepts DNA relevant to human genetic disease and focuses on genes, clones that identify restriction fragment length polymorphisms (RFLPs), and segments of importance in genetic linkage analysis. The ATCC collects well-characterized probes from investigators, expands and verifies the probes, and stores multiple samples that are distributed to interested investigators upon request. The ATCC currently receives probes at the rate of 300 per year and expects to distribute libraries at the rate of 1,000 per year by the 5th year of the contract. Probes that are likely to be heavily requested are identified through contacts with the Human Gene Mapping Library at Yale University and the Human Gene Mapping Workshops.

Following this presentation, several participants commented on the changing technology for the production of cloned DNA and noted that the ATCC will have to keep pace with these changes. Dr. Dayton stated that initial efforts to explore automation of procedures are already under way.

Dr. Caroline H. Holloway provided an overview of the Protein Identification Resource (PIR). This data base, funded by the DRR's Biomedical Research Technology Program (BRTIP), collects information on protein sequences and facilitates the identification of unknown proteins. In addition, protein and nucleic acid information can be correlated, allowing the identification of

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proteins based on nucleic acid sequence. Online data bases also include GenBank and EMBL. PIR is located at the National Biomedical Research Foundation at Georgetown University and has 126 universities and nonprofit organizations signed up as online users. Dr. Holloway noted that the grant that supports PIR will terminate at the same time as the GenBank contract terminates, which provides an opportunity for making decisions about collaboration between these two data bases.

Next, Dr. Holloway summarized the status of Bionet, also funded by the BRTP, which allows users access to a number of biological sequence data bases, including GenBank and PIR; software tools; and an electronic bulletin board. Bionet is operated by Intelligenetics in Mountain View, CA, and there are 867 users who subscribe.

During the discussion period, several participants noted that DRR's experience with centers should be valuable to the Committee in its efforts to determine the requirements for centers in the human genome project. There was also discussion of the differences among the grant, contract, and cooperative agreement mechanisms at NIH. Dr. Katherine L. Bick, of the Office of Extramural Research, NIH, provided clarification of these differences.

Dr. Judith Greenberg described the activities of the Human Genetic Mutant Cell Repository, an NIGMS-funded repository at the Coriell Institute for Medical Research in Camden, NJ. The Repository, also known as the Cell Bank, provides high-quality, well-characterized, contaminant-free cultures of cell lines from individuals with genetic disorders and from normal individuals. The Repository contains 4,500 cell lines, primarily fibroblasts and lymphoblasts, representing a variety of monogenic and multifactorial disorders. Chromosomal abnormalities such as duplications and deletions are also represented as well as hybridomas and myelomas. Gene mapping accounts for 12 percent of the Repository's utilization, while other utilization includes studies on the following: regulation of gene expression, cell physiology, mutagenesis, carcinogenesis, DNA synthesis and repair, and pharmacology.

Dr. Greenberg reported that, in January 1989, NIGMS awarded the Coriell Institute for Medical Research a 5-year, \$5.7-million contract to continue operation of the Repository. The Repository will undertake additional activities under the new contract. For example, it will make DNA preparations from selected cell lines for distribution to investigators, which will enable distribution of DNA from somatic cell hybrids.

Following this presentation, the desirability of duplication between the Repository's pedigrees and those maintained by the Centre d'Étude du Polymorphisme Humain (CEPH) was proposed as an item for the Program Advisory Committee's consideration, given that linkage mapping is a high priority in the human genome project.

The meeting continued with an overview of genome activities in agencies other than NIH. Dr. Benjamin J. Barnhardt provided background on DOE's Human Genome Initiative, which has been undertaken to expand DOE's ability to investigate the health effects of radiation and energy-related chemicals. He stated that DOE's Human Genome Initiative encompasses three major objectives: development of resources, including overlapping sets of cloned DNA fragments prepared as

cosmids and yeast inserts; development of new mapping and sequencing technologies; and development of data base management systems, techniques for automated input of DNA sequences, and computational tools for analysis.

Dr. Barnhardt stated that DOE's intramural effort in the Human Genome Initiative is largely represented by three national laboratories: the Lawrence Berkeley Laboratory and the Los Alamos National Laboratory, which have been designated as human genome centers, and the Lawrence Livermore National Laboratory. Dr. Barnhardt highlighted other DOE-supported activities, including preparation of chromosome-specific libraries for ATCC, involvement in the National Gene Library Project, and partial support of GenBank. He stated that future goals of the Human Genome Initiative are to complete construction of linearly ordered DNA clones for chromosomes that have already been started and to initiate the construction of such clones for additional chromosomes.

During the discussion period, Dr. Barnhardt noted that DOE does not fund training directly but that the human genome centers provide training indirectly. He also described ongoing efforts at Los Alamos National Laboratory to promote technology transfer to the private sector.

Dr. George F. Cahill, Jr., summarized the genome-related activities of the Howard Hughes Medical Institute (HHMI). He stated that HHMI spends approximately \$40 million per year to support investigators involved in genetics research, including those working on *Drosophila* genetics. In addition, the Institute provides support for medical students in research as well as for doctoral trainees.

Dr. Cahill stated that HHMI also funds genome resources at approximately \$3.5 million per year, including the Human Genome Mapping Library (HGML), the CEPH data base, and the Online Mendelian Inheritance in Man data base, among others. HHMI plans to investigate methods of making these data bases compatible with each other. Dr. Cahill remarked that HHMI will rely heavily on recommendations from the Program Advisory Committee regarding other areas of the human genome effort that need support.

Following this presentation, several participants reiterated the importance of designing data bases that can intercommunicate. They stressed that the Committee should play a role in developing guidelines that will minimize incompatibility in future data bases.

Next, Dr. John C. Wooley described the National Science Foundation's (NSF's) support for projects focused on infrastructure in genetics, for which \$50 million will be spent in FY 1989. He discussed five broad areas of special interest to NSF: instrument development, particularly during early stages; provision of instrumentation and facilities for genetic research; software development; basic genetic research (primarily on nonhuman organisms); and biological data bases. Specific NSF activities have included funding, in FY 1989, of a science and technology center dedicated to new technologies for DNA and protein chemistry. NSF is also involved in development of new software and algorithms for data base searching and development of special purpose hardware to increase the speed of biological data base searches. NSF has also collaborated with NIH to provide biomedical scientists access to resources at the NSF Advanced Computing Centers (Supercomputer

Centers). In addition, Dr. Wooley mentioned NSF's interest in the use of new technologies to advance research on corn and other agricultural plants and reported that NSF currently supports an RFLP effort in maize for \$300,000 per year.

Dr. Wooley stated that NSF is committed to technology transfer and to maintaining a "pipeline" of future scientists. Funds that support the biological research centers and the science and technology centers will also support multidisciplinary and interdisciplinary training activities at these facilities.

Discussion focused on specific details related to the science and technology center that was recently funded. Dr. Zinder noted that the administrative organization of the center may serve as a paradigm for future centers that may be established by the human genome program. The question of how to evaluate the progress of such centers was raised, and Dr. Wooley stated that the peer review system would play an important role in this area.

Dr. Robert M. Faust discussed the U.S. Department of Agriculture's (USDA's) interest in the human genome effort. He stated that USDA considers mapping of plant genomes a high priority and funds mapping studies on corn and soybeans at \$750,000. He also summarized recent advances in plant genetic research: Construction of RFLP marker genes has begun for corn, tomatoes, cabbage, and other crop plants; researchers have mapped three genes that control drought tolerance, five genes that have a major impact on flavor in tomatoes, and three genes involved with insect resistance in tomatoes; and a group of genes influencing yield in corn has been identified. Dr. Faust commented that USDA is interested in the human genome project primarily because of the technology that may result.

Dr. Faust also discussed the USDA Plant Genome Research Conference, which was convened in December 1988 to plan an initiative for mapping and sequencing the genomes of plants important to agriculture and forestry. Dr. Faust noted that the report developed at this conference is still in the draft stage; however, it mentioned development of a foundation of knowledge for plant science research as one of the initiative's goals. In addition, the draft report identified several criteria for selecting plants to map and sequence, including the following: Economic impact and domestic importance, maximum information transfer to other plant species, and provision of basic and fundamental insight. The draft report also mentioned features that should be incorporated in a national information network to support plant genome research: The network should be user friendly; should allow for all types of maps, quantitative information, and raw data; should be kept current through frequent updates and include a mechanism for data validation; and should be free or relatively inexpensive to users. Participants at the conference also recommended that an Office for Plant Genome Research be created at USDA to coordinate the Department's activities with other genome-related projects, such as the human genome program at NIH.

During the discussion period, several participants commented that USDA could aid the human genome effort by conducting mapping and sequencing of the genomes of agriculturally important organisms for comparative purposes.

The final segment of the first day of the meeting focused on international activities. Dr. Victor A. McKusick described the Human Genome Organization (HUGO), which was established in 1988 to facilitate international collaboration in the mapping and sequencing of the human genome. HUGO will also coordinate the efforts of investigators involved in mapping and those who work on sequencing and cloning. In addition, HUGO will coordinate research among investigators working on different species. Dr. McKusick stated that HUGO receives partial funding from HHMI but hopes to obtain multigovernmental as well as private funding.

Dr. McKusick reported that HUGO plans a wide variety of activities, ranging from international training programs to development of guidelines on ethical, social, legal, and commercial issues surrounding the human genome project. It will arrange for the exchange of data, samples, and technology relevant to genomic research and will assist in the organization and funding of the Human Gene Mapping Workshops.

There was brief discussion regarding inclusion of Third World countries in HUGO. Dr. Watson felt that, in order to keep costs down, representation in HUGO should be limited to countries that are actually doing the mapping and sequencing, rather than those interested only in the results. The Committee members stated that anyone who wishes to should be able to contribute to the human genome project.

Dr. Maynard V. Olson discussed Japan's endeavors in the area of human genome research. He reported that the Japanese have focused heavily on sequencing projects, in contrast to the approach generally taken in the United States, which is to concentrate on linkage and physical mapping, with a phase-in of sequencing as technological improvements materialize. Specifically, Japanese researchers have completed the sequence of chloroplast DNA and are currently coordinating a major effort to sequence the *E. coli* genome.

Dr. Olson noted that the interagency coordination situation in Japan is very complex, with various ministries, including the agriculture, education, and technology ministries, involved in mapping and sequencing projects. Nevertheless, Japan's hierarchal system lends itself to concentration on programmatic goals. He suggested that observation of Japan's coordination strategies may provide insights relevant to management of the human genome program in the United States.

During the discussion following this presentation, one participant noted that another aspect of Japan's management strategy has been successful coordination between academic and industrial laboratories, particularly with regard to data base management and software development.

Dr. Mark L. Pearson summarized the United Kingdom's activities in the area of technology development. He reported that British scientists have developed new techniques for the detection of sequence polymorphisms, i.e., polymorphisms between restriction sites. In addition, they have developed microsequencing methods for determining sequences at the end of restriction fragments, making it possible to generate large amounts of information that can facilitate the ordered overlapping of DNA sequences. In an effort to develop megabase-scale sequencing methods, British scientists are employing transputer technology as well as parallel processing methods that can handle

large blocks of sequences. Dr. Pearson also discussed the United Kingdom's large-scale mapping and sequencing projects, which have focused on the human genes CF, NF, and HD; viral genomes, including cytomegalovirus; plants, including *Arabidopsis*; and bacteria.

There was brief discussion following this presentation, during which the participants reiterated the need for international cooperation and sharing of data. They predicted a major role for HUGO in facilitating international communication and planning in genomic research.

Dr. Peter L. Pearson provided background on the European Economic Community's (EEC's) Predictive Medicine Program, which is planning a human genome analysis component. He reported that a working group consisting of two representatives from each of EEC's member states has been created to develop the program. This group has since been divided into the following six study groups: physical mapping, genetic mapping, advanced technologies, data base management, ethics, and training. He noted that EEC's human genome program plans to offer training fellowships that will allow less technologically advanced European countries to participate in and benefit from the program.

Dr. Pearson stated that the European approach to organization of the human genome effort involves coordination among laboratories through a network, rather than consolidation of projects in centers. It is anticipated that CEPH will form the center of the network, with which 20 European laboratories will be affiliated. Dr. Pearson also noted that a shared-costs financing arrangement will exist between EEC and laboratories that wish to participate in its human genome program.

During the discussion period, Dr. Pearson stated that coordination of effort among numerous laboratories would not preclude the possibility of two laboratories' working on the same task; in fact, he felt that a certain amount of overlap would be desirable.

There followed a general discussion of the first day's presentations. In an attempt to define the extent of interfacing activities that would be appropriate between the human genome program in the United States and similar programs in other countries, Dr. McKusick stated that the most important aspect of this interface will be exchange of data and biological resources. Such exchange would enable investigators to work more efficiently and would help to minimize duplication of effort.

Several participants sought clarification on the extent to which NIH plans to support human genome research abroad. Dr. Jordan responded by stating that NIH accepts applications for funding from foreign sources and has recently funded two foreign projects. Dr. C. Thomas Caskey commented that it is too early to contemplate major foreign funding and that resources must be kept within the United States until the U.S. program is well established. However, he stated that a small amount of money for "people movement" and collaboration between research groups would go a long way toward promoting cooperation and communication and, hence, acceleration of research.

Dr. David Botstein remarked that a spin-off of the U.S. human genome program is the long-term benefit that will be provided by the training component. A group of well-educated scientists will be poised to make use of the advances

and discoveries that result from the program. Dr. Olson concurred with the emphasis on human resources and stated that failure to address this issue adequately will lead to an "obsolete scientific personnel situation" in the future. He also cautioned against viewing acquisition of a data base containing the complete sequence of the human genome as the end point of the program. He stated that obtaining a reference sequence of the human genome will elevate the analysis of primary sequence data to a much more prominent position in biology, and predicted that state-of-the-art capability in this activity will be a prerequisite to being broadly competitive in basic research and biotechnology.

Dr. Zinder agreed with these comments and reiterated his earlier statement that sequencing of the human genome will be an "endless adventure." Following these remarks, he adjourned the first day of the meeting.

DAY 2

Dr. Zinder began the second day of the meeting by emphasizing the importance of the Advisory Committee to the human genome program. Next, he invited discussion of the biological scope of the program. The participants discussed the value of studying the genomes of model organisms at length. They agreed that the Committee should encourage such research for a number of reasons, e.g., advancement of sequencing technology and elucidation of the meaning of sequence information. They agreed in general that efforts should concentrate on five or six model organisms, preferably those for which genetic and physical mapping already have a strong start; however, several of the participants cautioned against a rigid definition of which organisms should be studied.

Dr. Watson raised the issue of the extent to which research in medical genetics should be supported by the human genome program. Dr. McKusick commented that the program is not capable of funding studies of all diseases with a substantial genetic factor. He felt that program support, at this stage, should be limited to studies on mapping of diseases that are both prevalent and caused by single-gene mutations. Several participants felt that projects in other diseases could qualify for program funding if they included the potential for technological or methodological advancement.

In terms of the technical scope of the program, the participants felt that the Committee should focus heavily on development of new technology and on making resources more available to the scientific community. Dr. Caskey emphasized the need to encourage investigation of the use of molecular biological tools in the field of cytogenetics.

The need for construction of new research space, particularly in connection with the establishment of centers, was discussed, and it was strongly urged that the Office of Human Genome Research should seek authorization to fund such construction.

Training was emphasized as an area in need of immediate attention, since the lead time required for setting up programs is likely to be lengthy. Several participants stressed the need for a forum in which students trained in biology-related disciplines, e.g., computer science, could receive training in biology, which would allow development of technological advances focused on

biological applications. Dr. Luther S. Williams of NIGMS announced that the Institute has recently launched a new training program in biotechnology that will employ an interdisciplinary, collaborative format.

Following this discussion, a working group on training was proposed, with Dr. Joseph L. Goldstein (chairman) and Dr. Leroy E. Hood as members.

Discussion moved to the topic of program management, and the advantages and disadvantages surrounding the creation of centers were debated. Dr. Olson commented that, since the Committee would not be able to micromanage numerous genome-related projects conducted by individual grantees, establishment of centers would probably be the best way to achieve programmatic goals. However, he stressed that such centers should be small and somewhat redundant in their activities, so that competition among them would insure progress. Dr. Phillip A. Sharp also supported the development of centers and noted that, in addition to providing a stimulating environment that promotes interaction among individuals, centers also provide a focus for attracting new resources.

Other issues raised in relation to centers were center-based training activities and industry participation. Dr. Zinder then proposed a working group on centers, with Dr. Phillip A. Sharp (chairman), Dr. Maynard V. Olson, and Dr. Cecil B. Pickett as members.

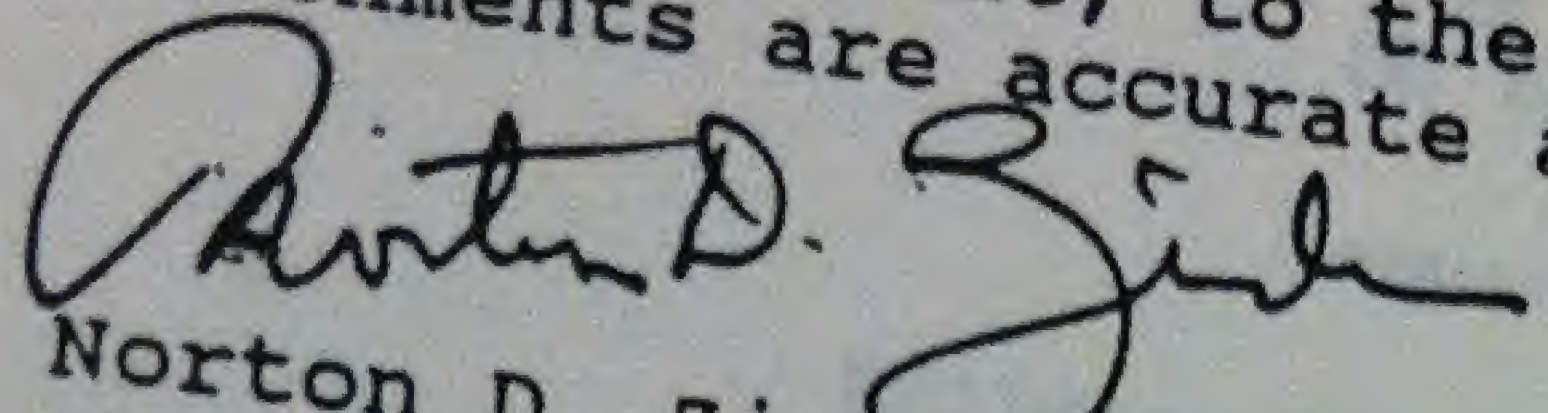
There was further discussion on program management, during which Dr. Watson stated that the relationship between the Office of Human Genome Research and NIGMS must be close and friendly but that the power to shape the human genome program through funding decisions should reside with the Office and its Advisory Committee. Dr. Kirschstein assured Dr. Watson and the Committee that NIGMS stood ready to assist them in achieving program goals and would carry out their decisions.

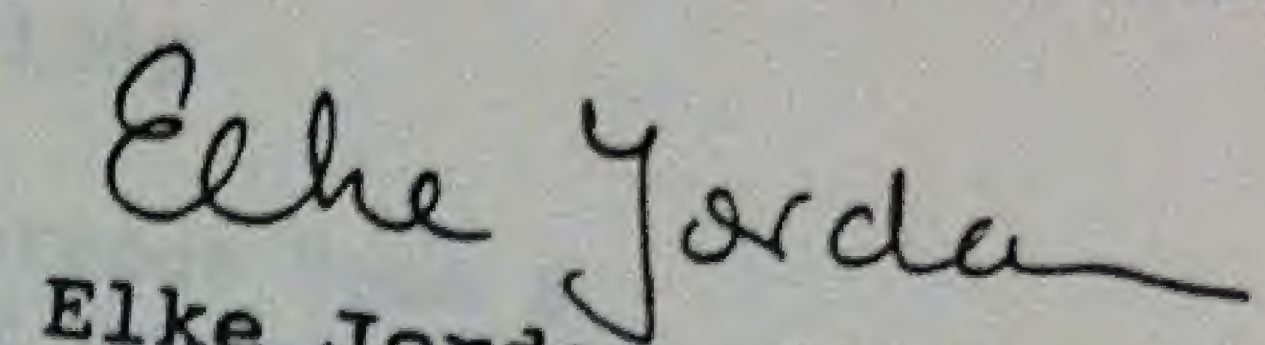
Next, Dr. Zinder moved to the topic of ethics. He estimated that, because of the high visibility of the human genome program and its potential impact on issues such as abortion and genetic screening, considerable program resources would be allocated for ethics-related work. He noted that the working group on ethics would become an important interface between the program and the public. Following these comments, he asked Dr. Nancy S. Wexler to chair the working group on ethics and also requested that Dr. Victor A. McKusick serve on this group.

Finally, a working group on data bases, which would examine extant data bases, formulate strategies for maximizing their usefulness, and examine the need for new data bases, was proposed. Dr. David Botstein was named chairman of this group. Drs. Jaime G. Carbonell and Mark L. Pearson were also appointed to this group, and Dr. George F. Cahill, Jr., was invited to serve *ex officio*.

After thanking the Committee members and the participants for their assistance in the preliminary efforts to launch the human genome project, Dr. Zinder adjourned the meeting.

I hereby certify that, to the best of my knowledge, the minutes and attachments are accurate and complete.

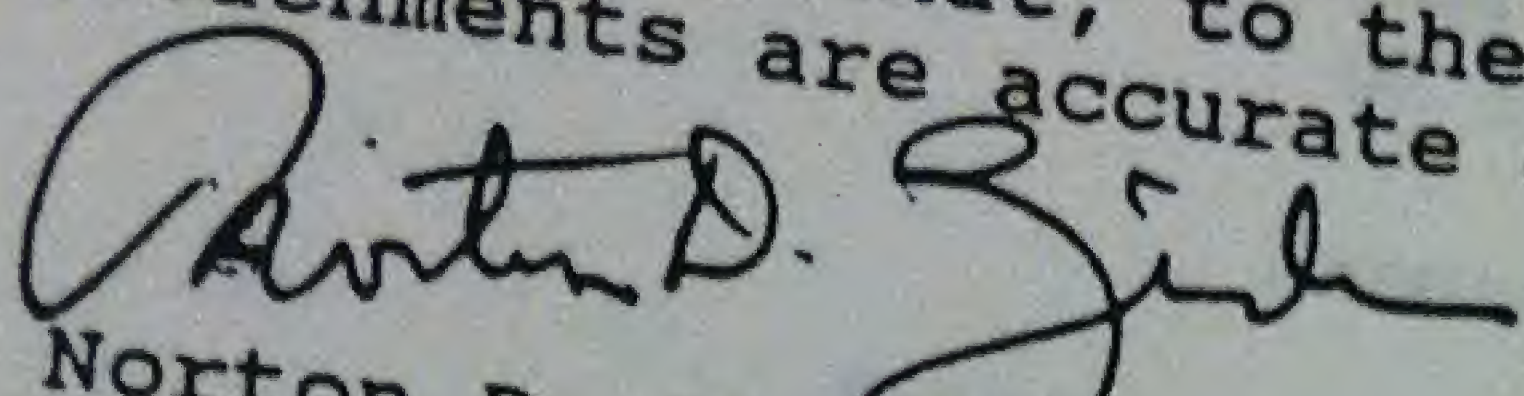

Norton D. Zinder, Ph.D.
Chairman

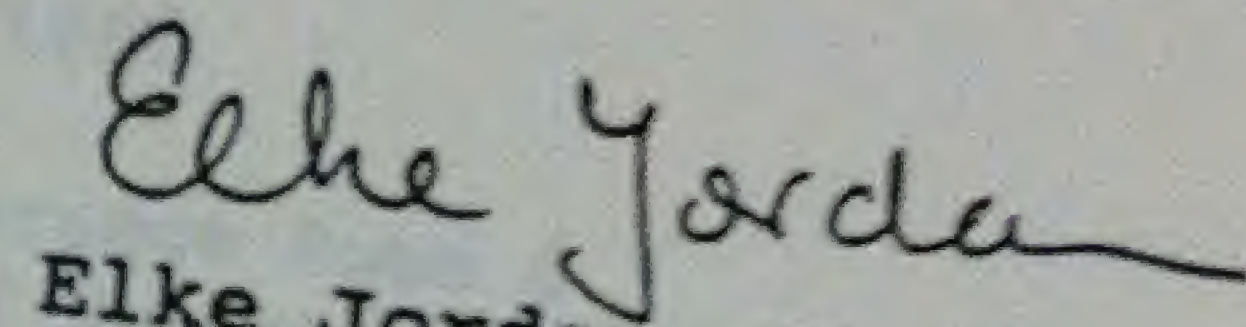

Elke Jordan, Ph.D.
Executive Secretary

These minutes will be formally considered by the Committee at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.

N.I.H. Program Advisory Docs

I hereby certify that, to the best of my knowledge, the minutes and attachments are accurate and complete¹.


Norton D. Zinder, Ph.D.
Chairman


Elke Jordan, Ph.D.
Executive Secretary

¹ These minutes will be formally considered by the Committee at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.

N.I.H. Program Advisory Docs

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January 3 and 4, 1989

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N.I.H. Project Meeting Docs

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January 3 and 4, 1989

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PROGRAM ADVISORY COMMITTEE ON THE HUMAN GENOME

January 3 and 4, 1989

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Larry Thompson
Washington Post

Michael Unger
Freelance

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Lisa White
The Blue Sheet

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Luther S. Williams
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David Wolff
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Wayne Wray
NIDR, NIH

Pam Zurer
Chemical & Engineering News

N.I.H. - Frequent Absence Docs

Program Advisory Committee on the Human Genome

June 19-20, 1989

Ramada Inn
Bethesda, MD

MINUTES

INTRODUCTION

The Program Advisory Committee on the Human Genome convened in Bethesda, MD, on June 19-20, 1989, to hear reports on genome-related activities at the National Institutes of Health (NIH) and other national and international agencies; to hear reports from the working groups established at the January 1989 meeting of the Committee; and to discuss the formulation of a plan for conducting the human genome project, which is due to be submitted to Congress in March 1990. The following Committee members attended:

Norton D. Zinder, Ph.D., Chairperson
Elke Jordan, Ph.D., Executive Secretary
Bruce M. Alberts, Ph.D.
David Botstein, Ph.D.
Jaime G. Carbonell, Ph.D.
Joseph L. Goldstein, M.D.
Leroy E. Hood, M.D., Ph.D.
Victor A. McKusick, M.D.
Maynard V. Olson, Ph.D.
Mark L. Pearson, Ph.D.
Cecil B. Pickett, Ph.D.
Phillip A. Sharp, Ph.D.
Nancy S. Wexler, Ph.D.

The following liaison members also attended:

Benjamin J. Barnhart, Sc.D.
George F. Cahill, Jr., M.D.
C. Thomas Caskey, M.D., F.A.C.P.
Mary E. Clutter, Ph.D.
Irene Eckstrand, Ph.D. (substituting for Ruth L. Kirschstein, M.D.)
Jerome Miksche, Ph.D. (substituting for Robert M. Faust, Ph.D.)

Dr. Miksche was unable to attend the second day of the meeting. The Committee roster and lists of speakers and others who attended are attached to these minutes.

N.I.H. Program Advisory Docs

Welcome and Administrative Remarks

Dr. Zinder welcomed the Committee members and participants, particularly Dr. Michael Kemp from the Medical Research Council in the United Kingdom, Dr. John Rodgers from the National Research Council in Canada, and Drs. Bronwen Lodei and Peter Pearson from the Commission of the European Community. He noted that there is worldwide interest in the human genome initiative, although there is also some opposition to it. He commented on the important role of the Committee in addressing concerns of both the research community and the public over issues such as diversion of funds from other important research and social/religious implications.

Dr. Watson's introductory remarks included a brief summary of the National Academy of Sciences' 1988 report "Mapping and Sequencing the Human Genome," which stated that initial efforts should focus on mapping; on model organisms to aid interpretation of data; and on procedures to reduce costs of sequencing. He noted that, currently, sequencing costs approximately \$5 per base pair, reduction of the cost to 50 cents per base pair is an objective. He also indicated that, with respect to mapping and sequencing, the unit of activity will probably be the chromosome. (This issue was discussed at length on the second day of the meeting.) He further speculated that, since many investigators in the field of genetics are "disease hunters," it may be difficult to encourage research on all the chromosomes.

Dr. Watson stated that mapping and sequencing of the human genome is "big science" in terms of the magnitude of data produced, making the participation of computer specialists knowledgeable in the field of biology essential. He noted the importance of construction to the program, so that institutions capable of conducting high-quality genome research can be given additional space and facilities in which to accomplish the work. He also stressed the importance of including a strong ethics component in the project, since the public will make decisions on how information about the human genome is used.

Dr. Jordan reported that a proposal has been submitted to the Secretary of the Department of Health and Human Services (DHHS) to elevate the Office of Human Genome Research (OHGR) to an organizational unit with funding capabilities. (This proposal was approved by the Secretary subsequent to the meeting.) She introduced new staff members who have joined the Office: Mr. James Vennetti, Acting Executive Officer; Ms. Michelle Coleman, Committee Management Officer; Dr. Bettie Graham, who will be in charge of the research grants branch; Dr. Jane Peterson (not present at the meeting), who will be responsible for the centers program; and Ms. Linda Engel, who will be in charge of the review component. Dr. Jordan also discussed the NIH's attempts to obtain authority for construction and noted that a legislative proposal to allow this has been submitted to the DHHS.

Approval of Minutes

Following these introductory remarks, Dr. Zinder called for a motion for approval of the minutes of the first Committee meeting, which was held on January 3-4, 1989. The motion was made and seconded, and the minutes were unanimously approved pending correction of the text concerning the European Community's (EC's) approach to organization of the human genome project (page 10, third paragraph). (The statements that laboratories will be coordinated "through a network" and that "CEPH [Centre d'Étude du Polymorphisme Humain] will form the center of the network" were incorrect; in fact, numerous networks will be established, and CEPH is anticipated to be a center in one such network.) Dr. Zinder then announced the dates of upcoming Committee meetings, which are as follows: December 4-5, 1989; June 18-19, 1990; and December 3-4, 1990. Dr. Watson noted that Committee

members who had been appointed originally for 1-year terms have been nominated for additional 4-year terms, and Dr. Jordan added that approval of these extended terms is pending and expected.

Reports of Significant Events

The meeting continued with reports of significant events related to the human genome program. Dr. Mark Guyer described the main features of the following meetings:

- An NIH meeting entitled "Human Genetic Maps," organized by the OHGR, was held on February 16-17, 1989. The purpose was to explore ways to reconcile and further develop linkage maps and ways to relate these to developing physical maps. Dr. Guyer noted that significant improvement in mapping techniques, including development of new types of polymorphisms to be used for linkage analysis, was evident from discussions at this meeting. Dr. Peter Pearson added that an important recommendation resulting from the meeting was for large research projects as opposed to "cottage industry." He stated that the participants also discussed the speed with which data should enter the public domain and added that compiling data from numerous laboratories can be a slow, difficult task.
- The Chromosome 11 Workshop, which took place on March 22-23, 1989, was sponsored by the National Institute of General Medical Sciences (NIGMS) and organized with the help of the chairpersons of the Chromosome 11 Committee of the Human Gene Mapping Workshops. One goal of the Workshop was to encourage the development of a physical mapping community for investigators involved in work on this chromosome in order to facilitate the exchange of information and materials. Approximately 80 percent of the laboratories involved in work on chromosome 11 sent representatives to the Workshop.

A similar workshop on chromosome 16 was held early in June 1989. As with the Chromosome 11 Workshop, the participants appeared enthusiastic about opportunities to collaborate. Approximately six more workshops of this type are planned, as well as another chromosome 11 workshop, which is scheduled for the spring of 1990.

Dr. Guyer noted that these meetings on mapping helped to "move the field along" and provided opportunities for resolution of common problems. He then discussed several additional meetings:

- The *E. coli* Database Workshop, held in March 1989, was the first in a series being sponsored by the National Library of Medicine (NLM) and the National Science Foundation. This workshop brought molecular geneticists and computer scientists together with the goal of defining problems and needs in the field of *E. coli* biology that might be addressed by the development of databases. There will be a followup meeting in late June 1989, where these needs will be prioritized and the computer scientists will determine which can be met by existing technology and which will require new developments.

Dr. Guyer also noted that genome-related databases for *Drosophila* and *C. elegans* have been discussed at recent national meetings, and workshops similar to the one on the *E. coli* database are planned.

- A workshop entitled "Nomenclature for Physical Mapping," which met on April 13-14, 1989, was cosponsored by the U.S. Department of Energy (DOE), the Howard Hughes Medical Institute, and the NIH. This meeting was the first in a series intended to discuss specific areas related to the management of physical mapping data. One of the conclusions of the workshop was that the name assigned to an element, such as a probe or a contig, should be unique and immutable and

The final draft of the workshop's recommendations will be widely circulated in the scientific community in order to obtain feedback prior to a followup workshop to be held in midautumn 1989, when the final recommendations will be prepared. The recommendations will then be published in scientific journals, and journal editors will be encouraged to assist in their implementation.

Dr. Clutter briefed the Committee on the results of the May 30, 1989, *Arabidopsis* Workshop, sponsored by the National Science Foundation to discuss the feasibility of mapping and sequencing the *Arabidopsis* genome. The participants reached the consensus that the project should be undertaken. Dr. Clutter added that a meeting is scheduled for July 20, 1989, at Cold Spring Harbor, NY, to discuss a plan for the project, and that there will be an international meeting (the International *Arabidopsis* Meeting) in October 1989. She estimated that 5 to 10 years and a total of approximately \$70 million will be required to complete the project. Dr. Watson noted that the United Kingdom plans to spend approximately \$12.5 million over a 3-year period for research on *Arabidopsis*. He also commented on the fact that plant research in the United States has been poorly funded compared to animal research and urged greater support of plant research in the United States. He also pointed out the need to plan U.S. research on *Arabidopsis* in context with the EC's efforts.

Dr. Jerome Miksche commented that the U.S. Department of Agriculture (USDA) is also interested in participating in the *Arabidopsis* genome project. He then highlighted a variety of agricultural challenges that must be addressed, including water quality, climatic changes, sustainable agriculture, the need for new crops, new uses for crops and forest products, food quality and safety, germ plasm enhancement, and the need for alternatives to chemical pesticides, and he stressed the necessity of finding genes associated with these activities. He commented on the meager funding of plant genome research and then discussed the implementation of two recommendations of the USDA Conference on Plant Genome Research, held on December 12-14, 1988: (1) The establishment of the USDA Office of Genome Mapping and (2) the formation of a coordinating committee for science and technology. Dr. Miksche gave a detailed description of the composition and function of this committee, which comprises the following six subgroups: computer and data management; genetics and breeding; restriction fragment length polymorphism (RFLP) mapping and gene tagging; molecular genetics; physiology and biochemistry; and biotechnology endpoints. He stated that this coordinating committee is scheduled to meet on August 30-31, 1989, to refine the goals and scope of the USDA's plant genome projects and to address questions such as the following: Is more information needed on physiology, biochemistry, and underlying agricultural problems, e.g., water quality, drought, and other environmental stressors? Should research focus on specific genetic traits? Should the project define specific plants as model systems? What funding mechanisms are appropriate? Should facilities and technology development be funded? He added that the USDA's plant genome efforts will span a 10-year timeframe and will cost over \$500 million. He emphasized that awards for projects will be made through a peer-reviewed grant program available to all scientists, extramural and intramural.

During discussion of this presentation, Dr. Joan Lunney of the Agriculture Research Service, USDA, mentioned that the USDA also has an active animal science component interested in genome research, and Dr. Miksche agreed that this will be a growing area in the USDA.

Dr. Olson described an international meeting held in March 1989 in Japan that discussed molecular approaches to the human genome. He reported that there was extensive discussion of model organisms, mapping and sequencing technology, human diseases, and general molecular genetics. He offered his perceptions on the status of genome analysis in Japan, stating that the existence of an advanced, monolithic plan is a misperception in the United States. He noted that basic research in biomedical science has been severely underfunded in Japan, so diversion of scarce resources is a major concern there. He also discussed Japan's *E. coli* sequencing project, an organized pilot effort that funnels support for research into academic laboratories interested in this work. He then described a

...ization project geared toward streamlining the sequencing process by using the polymerase chain reaction (PCR) for the preparation of sequencing templates. He stated that this project is relatively small but that contracts with industry will be the next step if scaleup is warranted. He added that review of the success of this project will be rigorous.

Dr. Olson proceeded to summarize results of the second Cold Spring Harbor meeting organized to discuss mapping and sequencing of the human genome, noting that a "powerful coalescence of excitement" toward the project and "solid evolutionary improvement in techniques" were evident. He stated that, although there was no sign among any of the existing projects on chromosomes of the development of convergent physical maps, it was clear that better methods of ordering the various entry points for physical mapping of the genome, e.g., short probes, contigs, etc., along the chromosomes have been developed. Dr. Charles Cantor of Columbia University and the Lawrence Berkeley National Laboratory added that the Human Genome Organization (HUGO) Executive Committee, which was polled following the workshop, unanimously endorsed an annual meeting of this type, to be held at Cold Spring Harbor.

Dr. McKusick discussed the Human Gene Mapping Workshops, the first of which was held in 1973 and attended by 70 persons. He stated that these workshops are currently held every 2 years for the purpose of collating the accumulated information on the locations of specific genes on chromosomes. They focus on data but have plenary sessions on methodology and applications. There are individual chromosome committees as well as committees on generic topics, e.g., nomenclature. He stated that the committee model has been useful and may indicate a need for permanent committees to collect this information on an ongoing basis.

Dr. McKusick noted that 700 persons registered to attend the 10th Human Gene Mapping Workshop (HGM 10), which was held in mid-June 1989. He estimated that, based on data from this meeting, approximately 1,700 genes have been assigned to chromosomes or chromosome regions. He added that this workshop ran smoothly due to the preliminary data collection and planning accomplished at HGM 9.5, which took place in September 1988. He also attributed the success of HGM 10 partially to efficient use of computers and dissemination of abstracts to the committee chairpersons prior to the meeting. He stated that HUGO will provide the administrative basis for future HGM Workshops as well as for mouse gene-mapping workshops.

Dr. McKusick also updated the Committee on recent HUGO activities, stating that the Organization is incorporated in Geneva and has established three continental offices: one in London, one in Bethesda, and one in Osaka. He reported that HUGO has 220 elected members, including Dr. George Cahill, who was recently elected treasurer.

Dr. Barnhart reported on activities of the DOE regarding the human genome initiative. These activities included development of a quarterly newsletter and an electronic bulletin board to facilitate communication between the DOE and its contractors and grantees. He reported that there have been three Steering Committee meetings, the third having been held in April 1989. He noted that one of the topics of discussion at that meeting was the establishment of the joint DOE/NIH planning subcommittee. In addition, the Steering Committee decided to conduct a workshop where contractors and grantees can provide the DOE with an overview of their projects. This workshop is scheduled for November 3-4, 1989.

Dr. Barnhart also stated that the Steering Committee has established a working group to consider issues related to sharing of biological materials, particularly the distribution of arrayed cosmid libraries (which are in demand). Major questions need to be answered: Who should distribute these libraries, and how can the costs of distribution be recovered? Dr. Anthony Carrano, of Lawrence Livermore National Laboratory and the chairperson of this working group, explained that these libraries have not yet been characterized, and good quality control data have not yet been established. He added that the

libraries have been distributed to test laboratories but that it has been difficult, in some cases, to obtain feedback from them.

Dr. Watson added that he has endorsed a proposed brief moratorium on the distribution of arrayed cosmid libraries until a policy addressing these problems can be developed. Several Committee members objected to the proposal, however, stating that providers of research materials have an obligation to provide other investigators with the materials on which their research conclusions are based. They urged that any proposed limitations on distribution should be approached in a sensitive manner. Dr. Watson assured the Committee that its opinions on this issue would be taken into account. (This topic was discussed further on the second day of the meeting.)

Dr. Peter Pearson described recent activities of the EC's genome program. He stated that the program's final report was approved by the EC's Committee for Medical Health Research and that funding is expected in December 1989. He specifically mentioned the report's recommendation that physical mapping data become part of the public domain 1 year after being generated—a requirement that will be established by contract. He also noted that the genome program will eventually have the same organizational status as the EC's medical health research program and therefore will come under "new management." Dr. Pearson added that the EC's genome program contains an ethics study group, which will be a standing committee that will evolve with the program. He mentioned that Dr. Wexler, chairperson of the NIH Program Advisory Committee's ethics working group, will attend the next meeting of the European counterpart. In response to a question from the Committee concerning whether the EC's genome program would consider helping to fund programs involving foreign (e.g., Japanese or U.S.) investigators in conjunction with European teams, Dr. Pearson stated his belief that multigovernmental funding would strengthen genome-related projects.

National Center for Biotechnology Information

Dr. David Lipman updated the Committee on the efforts of the National Center for Biotechnology Information of the National Library of Medicine (NLM) to integrate several databases containing information on *E. coli*. These databases include a working relational database for various strains stored at the *E. coli* Stock Center, a 2-D gel electrophoresis database, and a dataset that integrates genetic and physical maps of *E. coli*. He also described the Center's efforts to develop flexible, general purpose software tools that will allow investigators to design software packages for their own needs. In response to a question from the Committee on the strategy for making software tools available to users, he emphasized that outreach is a major concern at the NLM. He stated that software developed at the NLM has been demonstrated at Federation of American Societies for Experimental Biology (FASEB) and Gordon Conference meetings and that a similar approach may be taken with the molecular biology software tools. However, he emphasized that key individuals at institutions are often helpful in communicating the availability of useful tools.

Dr. Lipman also discussed a proposed project to develop a database of unpublished yeast genome sequences to be used for conducting database searches. If this project is found to be feasible, it may become a general resource at the NLM for other organisms as well.

NIGMS Report

Dr. Irene Eckstrand reported that the NIGMS plans to spend over \$10 million to fund new grants by July 1, 1989. Awards to be funded are distributed as follows: 17 for mapping (both genetic and physical), including 10 for human chromosomes and 7 for model systems; and over 20 for technology development, including 5 for sequencing technology, 3 for computer technology, and 16 for other technological innovations. She stated that the NIGMS also plans to award supplements to stimulate the

development of physical mapping databases for specific chromosomes. She added that remaining monies would be used to support OHGR activities and special projects.

Following this presentation, there was discussion regarding the priority scores of the applications that had been received. Dr. Eckstrand stated that awards were made on the basis of the importance of the projects to the human genome program as a whole (not rigidly on the basis of priority scores). She estimated that approximately one-third of the proposals received were funded. Dr. Caskey commented that Dr. Watson's proposal of limiting the term of genome-related grants to 3 years had been presented to the National Advisory General Medical Sciences Council but was not accepted; the consensus of the Council was to adopt the recommendations of the study sections concerning individual grants.

Reports From Working Groups: Center Grants, Training Grants, Databases, and Ethics

The meeting continued with reports from the working groups established at the January 1989 Committee meeting. Dr. Sharp presented the recommendations of the working group on center grants, which consisted of Drs. Richard Axel, Ronald Davis, Daniel Nathans, Maynard Olson, Cecil Pickett, and Dr. Sharp himself as chairperson. The group proposed that the NIH use the core center grant mechanism (P30) to support the infrastructure for genome research at qualifying institutions. He stated that the center grant envisioned by the working group would be similar to that of the National Cancer Institute and would have the following eligibility requirements: The institution must have significant ongoing research on genome-related projects and a specific long-term objective, e.g., physical mapping of particular chromosomes; it must be domestic and can be academic, nonprofit or for profit; it should preferably be a single institution, although consortia will be eligible; and it should be willing to collaborate with industry, since the private sector has resources that may help achieve the goals of the human genome program. He added that the working group recommended a 5-year term for this type of grant, with review 3 years after initiation to allow for a 2-year phaseout of unsuccessful centers. The Committee accepted these recommendations.

Dr. Sharp stated that core centers funded by this mechanism would provide the following: a stable environment for large-scale undertakings, which would include projects funded by other NIH mechanisms as well as other sources; opportunities for interdisciplinary collaboration, rapid dissemination of information, and sharing of resources; an administrative structure to facilitate collaboration with the private sector and recruitment of new investigators; and core facilities, e.g., for DNA and protein sequencing.

Dr. Sharp estimated that between \$5 and \$10 million will be required to operate each center but emphasized that the centers will attract funds from sources other than the human genome program.

Dr. Goldstein discussed the recommendations of the working group on training grants, which included the following members: Drs. Donald Brown, William Gelbart, Joseph Goldstein (chairperson), Leroy Hood, Gene Myers, and Luther Williams (*ex officio*). The group suggested three types of training grants in genome research: predoctoral institutional grants, individual postdoctoral grants, and senior fellowships for established investigators. The group recommended that two-thirds of the 185 training slots proposed in the FY 1990 budget for the human genome program should be for predoctoral institutional training, although Dr. Goldstein noted that the distribution would depend somewhat on the numbers of applications submitted for each type of grant. Dr. Goldstein stated that the theme of all these grants should be the transfer of information from one field to another, e.g., from computer science to molecular biology and vice versa. The Committee accepted these recommendations. There followed a discussion of the importance of talented technicians to the human genome initiative, during which several Committee members noted that there is a need to support good programs that train such individuals. Dr. Zinder asked the working group to reconvene to consider whether the human genome program should support training for career-level technicians.

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In response to a question concerning the relationship between the human genome program's proposed training grants and those of the NIGMS, Dr. Jordan replied that there may be some overlap between the two agencies but that the genome program's training grants would focus on interdisciplinary components. She added that the OHGR would coordinate training activity closely with the NIGMS.

Dr. Botstein, chairperson of the database working group (Drs. George Cahill* (*ex officio*), Jaime Carbonell, and Mark Pearson) presented the group's recommendations. The database working group agreed that, in the short term, the scientific community needs a minimal database containing all published nucleotide and amino acid sequences, with information no more than 1 month behind the published literature. Dr. Botstein stressed that this database would provide minimal annotation but would use a format that would allow the data to be incorporated into future databases. Dr. Liptman commented that the NLM is currently developing an experimental "backbone" database similar to what the working group proposed, using information from MEDLINE and working with experts from GenBank and the Protein Information Resource. He added that multiple approaches for information retrieval are planned for this database and that linkage with other databases is also a goal. Dr. Botstein stated that the working group would prepare recommendations on long-term needs in time for the December 1989 Committee meeting. The Committee accepted these recommendations but asked the working group to consider issues related to administration of the sequence databases, specifically the roles of the NLM and the OHGR. In this regard, it was requested that the NLM prepare a position paper describing how it envisions its role in the genome project for review by the working group and the full Committee. There was also agreement that the database working group of the NIH Program Advisory Committee on the Human Genome would work with the DOE's informatics group and possibly an international group when funds from Europe become available.

Dr. Wexler discussed the activities of the ethics working group, whose members included Drs. Jonathan Beckwith, Robert Cook-Deegan, Patricia King, Victor McKusick, Robert Murray, Thomas Murray, and Dr. Wexler as chairperson. Dr. Wexler stated that the working group plans a series of interdisciplinary workshops to focus on specific issues related to the ethical, genetic, social, and legal implications of the human genome initiative for society. The first such workshop, planned for November 1989, will recommend the overall research agenda and attempt to identify issues that need to be addressed. The working group also recommended that public testimony and town hall meetings be held to "take the temperature" of the public with regard to the human genome program. She stated that the Alliance of Genetics Support Services will provide assistance in setting up these meetings.

Dr. Wexler reported that, in March 1989, she had sent a letter to various professionals involved in law, ethics, and genetics soliciting their opinions on genetics issues. She indicated that, overall, the letters she received in response were positive and highlighted the following points:

- The letters urged the Committee to consider history and precedent in order to avoid repeating the mistakes of the past. They alluded to the experience of Nazi Germany and the history of social Darwinism in the United States.
- They mentioned the unique nature of the human genome project, which will result in the capacity to predict a disease process in an individual.
- The letters advised making use of the media in order to let both the professional community and the general public know about the program and its activities.

*Dr. Peter Pearson substituted for Dr. Cahill at the meeting of this working group.

- They raised questions concerning whose genome will be sequenced: Will there be differences between ethnic and racial groups? Will there be generalizability across groups?
- They pointed to the common understanding of "good" and "bad" genes that could cause individuals or disorders to be seen as stereotypes, whereas genetic problems should be seen as part of the general variety of human features.
- They cautioned against genetic reductionism (trivialization of the complexity of genetics—which might lead to a deemphasis of the impact of free will and a tendency toward genetic determinism).
- They raised issues of privacy and confidentiality, particularly for database families, such as the CEPH families, who are being used for genetic mapping studies. For example, if an individual is found to be at high risk for a particular disorder, should there be a provision for notifying the individual?
- The letters noted that there will be a lapse between the ability to screen for genetic disorders and the ability to treat these disorders. They advised the human genome program not to promise too much: while molecular biology offers a hopeful avenue toward treatment, cures for genetic disorders will not be available immediately.
- They pointed out insurance issues; e.g., will an insurance company have to pay benefits for an affected infant whose mother knew about the genetic disorder through prenatal genetic screening but chose to carry her pregnancy to term?
- They discussed the problem of how to integrate new genetic knowledge into mainstream medicine and the concomitant implications for malpractice issues.
- They raised the possibilities of stigmatism at the workplace and job discrimination against those prone to disorders.
- They expressed the concerns of handicapped rights groups, who are already sensitive to society's perceptions of handicapped persons, including the concern that a program to predict and prevent genetic handicaps in a sense makes the statement that people with these types of handicaps are not welcome in our culture.

Dr. Wexler stressed that, because the human genome initiative will lead to increased genetic screening capabilities and the ability to predict diseases in individuals, the program must emphasize the hopeful perspective that knowledge of the molecular basis of a disease can lead to treatment possibilities. She also emphasized that the budgets of the categorical Institutes of the NIH must be kept commensurate with that allocated for sequencing of the human genome, since these Institutes will play a major role in making use of the knowledge gained through the genome effort.

Dr. Jordan provided an overview of the types of enquiries that have been received in response to a program announcement, published on March 3, 1989, requesting proposals for research on ethical and legal issues relevant to the human genome program. She stated that the interests of the applicants varied widely, ranging from standard ethical investigations to studies of historical precedents, genetics and the law, and genetics and religion. She added that there were also applications dealing with educational approaches and conferences. She indicated that the OHGR looks forward to input from the ethics working group on specific areas on which the Office should focus.

Dr. Zinder then named the NIH representatives to the NIH/DOE joint subcommittee and planning group as follows: Drs. David Botstein, Jaime Carbonell, Maynard Olson, Mark Pearson, Nancy Wexler, and Norton Zinder. This joint subcommittee will participate in a planning retreat to work on a proposal for the overall strategy of the human genome initiative to be held this summer. He also listed the names of those anticipated to represent the DOE on this subcommittee: Drs. Sheldon Wolff, Mary Lou Pardue, Leonard Lerman, Charles Cantor, Anthony Carrano, and George Bell. Dr. Zinder noted that Drs. Lipman and Caskey, among others, would be invited to participate as consultants.

Other New Initiatives: Equipment, Intramural Research, and Physical Mapping Databases

Dr. Jordan announced that the OHGR proposes to solicit applications for supplementary funds for the purchase of equipment. Any NIH grantee working on the genome project may apply, but there must be at least 2 years of funding remaining in the grant at the time of submission of the application. (A Committee member commented on the large number of 3-year grants that have been awarded and suggested that only 1 year of remaining funds should be required.) Since this solicitation is designed to address the gap in funding for medium-priced instrumentation, the limit per item or per grant will be \$100,000. Dr. Guyer briefly described a proposed Request for Applications (RFA) to support initial development of databases designed for physical mapping data. The Committee supported both these initiatives.

Dr. Jordan described a proposed NIH intramural research program whereby intramural investigators may receive funding to expand their activities in order to participate in the human genome program. She stated that, in contrast to a similar mechanism in the NIH AIDS Program, which has funded many small projects, collaboration on large projects will be encouraged. When asked whether applications from intramural investigators would be reviewed by the same study sections that review extramural proposals, Dr. Jordan replied that that would be technically difficult but that a comparably rigorous review for the intramural proposals would be conducted. Several Committee members insisted that the quality of intramural projects must be comparable to that of extramural projects. Drs. Watson and Jordan assured the Committee that every effort would be made to ensure that.

TUESDAY, JUNE 20, 1989

Program Budget

The second day of the meeting began with a brief presentation by Dr. Watson on the human genome program's budget. He indicated that the FY 1990 budget proposed by the President is for \$100 million. He stated that the allotment in this budget for research center grants is \$10 million, that he hoped this would increase in FY 1991, and that 10 centers would be funded by FY 1991. He added that funds for training will also probably increase in FY 1991. He reported that congressional approval of the budget is expected by the end of the fiscal year.

General Discussion

There was brief discussion on whether the Committee should establish a technology development working group. Dr. Jordan inquired as to whether the Committee perceived impediments in the funding mechanisms for technology development. Dr. Hood replied that attitudes of study section members regarding what constitutes "good science" can cause obstacles in this area and emphasized the need for

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The Committee explored further the proposed establishment of research centers. A Committee member inquired as to whether one or two investigators who wished to manage a large group of investigators (30 or more), all working on a specific project, would be eligible for a center grant. Dr. Watson replied that other mechanisms, e.g., research contracts, would be more appropriate for this type of endeavor. In response to a question from the Committee concerning whether the centers would come under multiple reviews due to the various mechanisms that will contribute funds, Dr. Sharp stated that there would indeed be a bureaucracy and multiple reviews; however, because of the stability of the overall center, the failure of one component would not destroy the whole group. He noted that skilled personnel could be retained over long time periods through support from various sources, including partial support from the center grant, through the core facilities, through R01's (individual investigator grants) or P01's (program project grants), or through direct contracts.

The members discussed the possibility of centers' contracting with industry for services, which raised conflict-of-interest issues. While it was pointed out that most academic institutions have conflict-of-interest policies, the Committee members noted that institutions' guidelines vary greatly. Dr. Jordan stated that the centers would not be allowed to subcontract without approval by the NIH, and Dr. Botstein suggested that perhaps a clear statement of policy from the Committee would be sufficient to address conflict-of-interest concerns. Dr. Zinder requested that several Committee members (Drs. Alberts, Goldstein, Pearson, and Pickett) research the conflict-of-interest and disclosure guidelines at representative institutions and present information for discussion at the next Committee meeting.

New Issues: Model Systems, Rothman Proposal, Gene-Mapping Services, Hybrids, and Others

The Committee discussed at length the proposed revision of a program announcement that is intended to consolidate two broad program announcements and several RFA's that were previously published; to indicate the NIH's interest in technology development applicable to the human genome initiative; and to specify model organisms of special interest to the program, i.e., *E. coli*, *S. cerevisiae*, *D. melanogaster*, *C. elegans*, and *M. musculus*. There was significant debate on whether the wording concerning the model organisms was too restrictive, discouraging valuable research on other organisms. Several Committee members favored broadening the focus and suggested wording such as "*E. coli* and other selected prokaryotic organisms." Others believed that, if projects on many organisms are begun, few will be completed. Still others favored a narrow focus with respect to technology development applications, stating that investigators on these projects should be encouraged to work on one of the model organisms designated in the program announcement. Drs. Jordan and Guyer emphasized that the intent of the announcement was not to exclude research on other organisms but to put the burden of demonstrating the value of such research to the human genome program on the investigator. The consensus of the Committee was to broaden the focus somewhat for now.

Dr. Watson proposed that approximately 25 percent of the program's budget be devoted to physical mapping of model organisms in the initial years of the project.

Dr. Zinder opened discussion of the proposal submitted by Dr. James Rothman, which suggests Government funding of biotechnology companies on a competitive basis to sequence the proteins in novel and complex cellular organelles. Under this proposal, the companies would also provide a number of other services, e.g., complementary DNA cloning of genes encoding the structures' proteins. This work would be performed under the aegis of a principal investigator, who would be able to use the resulting data for experiments. The Committee noted that the proposal would provide for the identification of new functional genes and might attract cell biologists to the human genome program; however, several members cautioned against uncoupling the biotechnology from the "real" biology, and

The Committee reviewed additional suggestions for support of gene-mapping facilities (submitted by Drs. Robert Sparkes, Thomas Shows, and Timothy Donlon) and resources for the development of somatic cell hybrids (submitted by Dr. David Ledbetter). Pointing out the rapidly changing technology in these areas and the fact that similar work is being carried out on regular NIH grants, the Committee decided against support on a larger scale.

Dr. Zinder reopened the topic of distribution of arrayed cosmid libraries currently produced primarily by the national laboratories of the DOE. Dr. Cantor stated that it would be counterproductive to halt the distribution of ordered arrays at this time. He added that ordered arrays will be distributed after they have been well characterized, although there are still unresolved issues concerning who will bear the costs of distribution and how data developed from use of the arrays will be collected. The Committee supported this view.

Dr. Watson informed the Committee of an opportunity to join British investigators working on sequencing the *C. elegans* genome. He indicated that the project would involve sequencing 13,000,000 base pairs per year and would take approximately 6 years to complete. He suggested that perhaps half this work could be done in the United States, and half could be conducted in the United Kingdom. He estimated that a 3-year grant of approximately \$600,000 per year would be needed to explore the feasibility of the project, provided an equal sum was contributed by the United Kingdom. He noted that the Medical Research Council would receive a grant proposal to help fund the United Kingdom's activities on the project, and Dr. Kemp stated that the Council was interested in this collaboration. Several Committee members commented that the project would offer a unique resource and pointed out that the community of investigators working on *C. elegans* already has an outstanding record of sharing information and materials. The Committee unanimously endorsed the concept of joint funding of such an effort.

Units of Scientific Management

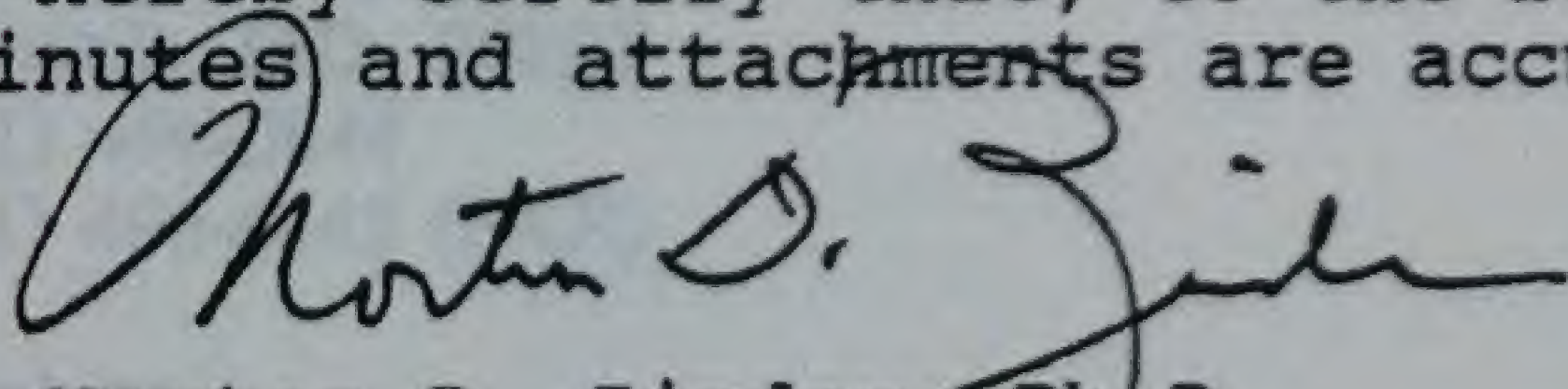
The Committee discussed Dr. Watson's proposal that the chromosome be the scientific unit of management for the human genome project. Several members strongly urged that, if this strategy is adopted, information that will be useful as better technology is developed must be collected and made available as a by-product of chromosome-oriented activities. They specified that the type of information that would be of long-term use would be sequences that uniquely identify pieces of DNA, and this information must be entered into the public domain so that any laboratory can use it. Dr. Zinder called on Drs. Hood and Olson to develop a specific proposal for how to address this issue prior to the next meeting and also for the establishment of journal publication standards that would include this requirement. Dr. Peter Pearson stated that the chromosome is "the only workable unit of management" at the infrastructure level, since work on a particular chromosome is specialized in terms of the standard tools (cell lines with break points, somatic cell hybrids, chromosome fragments, YAC's and cosmids, etc.) and expertise required for mapping and sequencing. He suggested that organization take the form of a consortium of laboratories that pool their efforts and data on an individual chromosome. Several members proposed the chromosome as the unit of database management but favored a *laissez-faire* policy for genome projects in the initial phase of the program; they supported a gradual coalescence toward organization by chromosome as the human genome project proceeds. Dr. Caskey suggested that the cooperative agreement would be a useful mechanism by which to facilitate such coalescence. Under this mechanism, the NIH would define the mission (in the case of the human genome program, the mission would be closure on a particular chromosome), and institutions and centers would compete for the opportunity to participate.

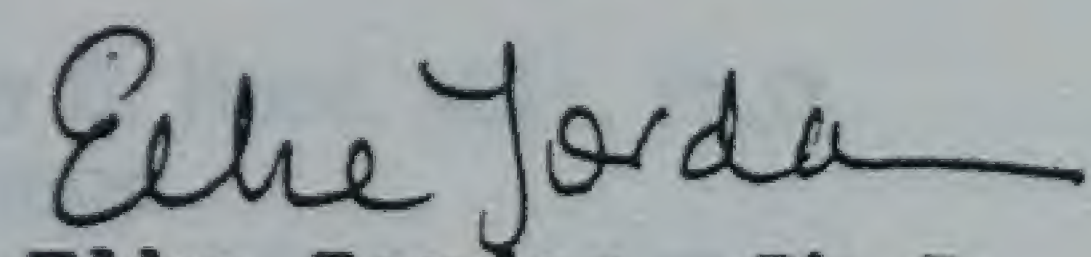
Dr. Zinder stated his belief that the program has an obligation to create a "value-free" system whereby all the chromosomes are studied, regardless of whether or not they contain genes associated with diseases. He asked for suggestions on alternative units of management if the chromosome is not to be the unit of management (there was general agreement on this) but rather when this level of organization and management should be implemented. Most of the members believed that competition and technology development should be the key components of the program's initial phase, while chromosome-by-chromosome management will be necessary to bring the project to completion. Others commented on various ways to encourage coalescence. Dr. Wexler mentioned the "convening power" of the NIH to bring scientists working on particular chromosomes together with those interested in technology development, and Dr. McKusick observed that the chromosome committee model has been useful in the physical mapping community. Dr. Watson also noted the trend toward the formation of chromosome groups but agreed that it would be premature to try to organize the project on a chromosome basis at this time. He stated that the program will sponsor chromosome workshops and that HUGO will play a role in facilitating international involvement. He added that leaders interested in managing work on entire chromosomes will probably emerge as a result of these workshops. He also stated that foreign countries will be encouraged to play a management role for some of the chromosomes when the program reaches the stage where this is necessary.

Adjournment

Dr. Zinder closed the meeting by thanking the Committee members and other participants for their contributions and inviting the individuals who are not scheduled to attend the planning retreat to communicate any ideas they may have to the representatives who will attend.

I hereby certify that, to the best of my knowledge, the minutes and attachments are accurate and complete¹.


Norton D. Zinder, Ph.D.
Chairman


Elke Jordan, Ph.D.
Executive Secretary

¹ These minutes will be formally considered by the Committee at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.

Second Meeting

Program Advisory Committee on the Human Genome

June 19-20, 1989

Ramada Inn
Bethesda, MD

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N.I.H. Program Advisory Docs

Second Meeting

Program Advisory Committee on the Human Genome

June 19-20, 1989

Ramada Inn
Bethesda, MD

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FG/GR/NI-06

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Report to the
Director,
National Institutes
of Health

AD HOC
PROGRAM
ADVISORY
COMMITTEE
ON COMPLEX
GENOMES

Reston, Virginia
February 29-
March 1, 1988

FG/GR/NI-06



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June 14, 1988

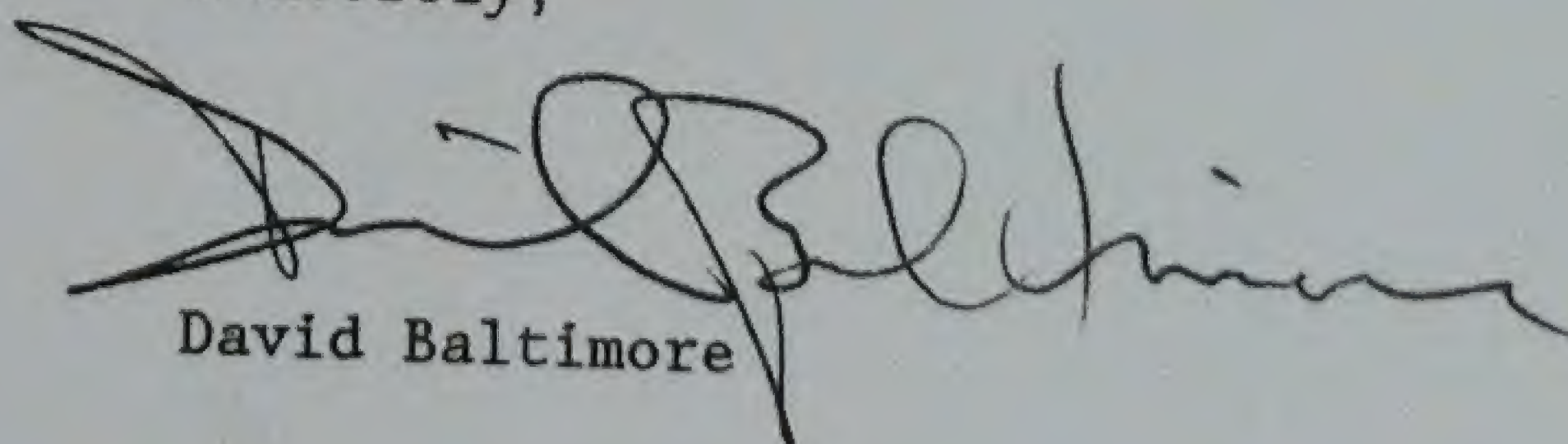
Dr. James Wyngaarden
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Dear Dr. Wyngaarden,

Enclosed is the final report of the NIH Ad Hoc Program Advisory Committee on Complex Genomes. This report, skillfully put together by an independent rapporteur and reviewed by the Committee members, reflects well and concisely the discussions at the single meeting of the Ad Hoc Committee that took place on 29 February and 1 March, 1988. Embodied in it are the major recommendations that emerged from the Discussions.

I trust that this document can serve as the basis for NIH to develop a vigorous program to exploit the opportunities in Genome Analysis that have arisen in the last few years. Such a program would complement NIH's other efforts in biomedical research and would lead our science into even-deeper understanding of how complex genomes are organized and the nature of the information they encode. By interdigitating NIH's efforts with those of other agencies and other countries, an international program of great power and importance should emerge.

Sincerely,


David Baltimore

R

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N.I.H. Program Advisory Docs

Right now, NIH has
\$23 million in current
GENOME research. It
will go to \$63 million
DOE has some \$17 million
in GENOME.

NATIONAL INSTITUTES OF HEALTH

RECOMMENDATIONS AND PRIORITIES DEVELOPED

BY THE AD HOC PROGRAM ADVISORY COMMITTEE ON COMPLEX GENOMES

N.I.H. Program Advisory Board

GENERAL POLICY ISSUES

The prospect of mapping and sequencing complex genomes, particularly the human genome, looms as an important challenge for the biological community. Discussions about the pace and strategy for best proceeding have sometimes been intense. But there is also growing recognition within the biomedical research community that parts of an informal program already have been taking shape because of rapid progress in molecular biology and genetics.

To assess these developments, Dr. James B. Wyngaarden, the Director of the National Institutes of Health, recently convened a group of experts as an Ad Hoc Program Advisory Committee on Complex Genomes (CCG)* (Attachment I). At a meeting late in February, the Committee expressed confidence that, by building on the groundwork now in place, a well planned effort to intensively analyze the human genome could bring dramatic success in a few years--and substantial completion of the project within a 15-year period. However, to meet this ambitious goal, the CCG believes that a systematic, centrally-coordinated initiative is required.

Many benefits would accrue from such a complete analysis of the human as well as other complex genomes. Besides the wealth of biomedical information this concerted effort will provide, enormous scientific and technological advances can be expected, having both basic and commercial applications. Many challenges lie ahead if this effort is to succeed, but it is likely to enhance U.S. competitiveness, particularly in the growing international arena of biotechnology.

The Ad Hoc CCG has developed a set of guidelines and recommendations for establishing a formal program within NIH, tentatively named the Human Genome Research Program. The Committee is well aware that plans for such a program are likely to evolve rather rapidly, particularly as expected technological developments pave the way for improved efficiency in different phases of this undertaking. Indeed, the members of the Committee did not reach consensus on some issues of significance. Nevertheless, CCG members agreed that certain priorities must be set now, and some principles for shaping the overall NIH program must be unequivocally established from the outset. They include:

- Peer review and permanent advisory committee. Stringent peer review will be vital during all stages of this project, with the emphasis on selection of the best scientific proposals put forth by scientists drawn from a broad base. Because the program will highlight special technology needs and unusual targeted efforts compared to other research components within NIH, special study sections should be established as needed. Moreover, a permanent Program Advisory Committee made up of expert scientists from appropriate disciplines will play a crucial role in keeping efforts on target.

* The NIH Ad Hoc Program Advisory Committee on Complex Genomes met February 29-March 1, 1988, in Reston, Virginia.

- Establish an Office of Human Genome Research. The Ad Hoc Program Advisory Committee unanimously endorsed a proposal to establish an Office of Human Genome Research, headed by a new Associate Director, within the Office of the Director of NIH. CCC believes that separate management of this new program not only will stress its unique identity, but will emphasize that it should not in any way disrupt other NIH research programs. The Associate Director and staff is expected to work closely with the permanent Program Advisory Committee, as needed, and to coordinate related efforts with representatives from all NIH components and elsewhere within the research community.
- Role of model systems in providing insights. Insights into human diseases will be rapidly forthcoming from this effort, and careful attention must be given to disseminating medically useful information to the wider community. Despite this obvious emphasis on human genetics, vital insights can and will be gained by continuing reliance on pertinent model systems—microbial, lower and higher animals, and even plants when appropriate scientific justifications are put forward. Considerable interplay is expected with other research fields, and free exchange of information and technologies must be fully encouraged at all levels.
- Rolling 5-year plan with annual review. Because the technologies for mapping, sequencing, and handling the biological materials and data to be generated are expected to change dramatically, an annual review and adjustment of program priorities are anticipated. Thus, although a tentative 5-year agenda should be set now, there must be ample flexibility to change tactics when new opportunities arise, particularly during the first few years of this enterprise.
- Training needs. Special attention must be given, particularly during the early phase of this program, to assessing and providing for the specialized training needs that such an interdisciplinary undertaking entails.
- National Academy of Sciences Report. The Ad Hoc Program Advisory Committee agrees with many additional recommendations outlined in the report, "Mapping and Sequencing the Human Genome" of the National Research Council of the National Academy of Sciences (February 1988) (Attachment II).

SPECIFIC PROGRAM NEEDS

The Ad Hoc Committee believes that the Human Genome Program represents a unique opportunity in modern biological research. The grand scale of the program makes the undertaking unique in biological research, and it also calls upon scientists with a uniquely wide variety of skills to work closely together. Moreover, the nature of the undertaking dictates that scientists representing different disciplines work cooperatively, with little or no hierarchical relationship. Thus, for instance, the insights of a computer scientist of a biochemist working on some seemingly obscure aspect

of a particular project could well prove vital to the entire program. Hence, proper attention must be given to streamlining communications among all participants and for encouraging a continuous exchange of ideas.

During the course of its deliberations, the Ad Hoc CCC scrutinized the prospective program by dividing it into four main activity areas: mapping, sequencing, information, and biological materials. Each of these groups developed goals and tentative plans for meeting them as well as projected costs for doing so (for projected costs, see Attachment III).

However, certain components of the program and the costs for meeting such needs are general, cutting across all the activity areas. The priorities identified by the CCC that transcend working group subject areas fall into two major categories—training needs and infrastructure and construction requirements. Key requirements include the following:

- The [Human] Genome initiative entails new training needs for scientists with interdisciplinary skills. To begin with, the program should be training 50 predoctoral students and recruiting 50 postdoctoral scientists—building over a 5-year period to 150 predoctorals and 150 postdoctorals.
- Provision must also be made for training master's and bachelor's level scientists and technicians, who will make valuable contributions to this overall program.
- Information handling will require a special component to encourage students to obtain coordinated training in both biology and computer/mathematical analysis.
 - Initially three to five such programs with three to five students each should be supported, building to 50 to 75 students per year after 5 years.
 - Training must extend to postdoctoral level scientists and senior visiting scientists, with the annual program initially set for about 20 postdocs and five visiting scientists but growing after 5 years to 50 postdocs and 10 visiting scientists.
- Some provision must be made for building and remodeling laboratory facilities, particularly as efforts are begun to conduct large scale DNA sequencing at the megabase level and beyond.
- Provision must be made for new administrative costs that arise from the program, including the efforts associated with the proposed new Office of Associate Director and staff, a permanent Program Advisory Committee, and new study sections devoted to reviewing Human Genome Program proposals.

Mapping and Sequencing

The Ad Hoc CCG carefully examined the specific scientific and technological tasks that make up the new Human Genome Research Program. Although the overall goals of the program are well defined, many of the intermediate achievements will necessitate adjustments along the way. Because much of this anticipated development will lead to improved and more efficient methodologies, the Committee members stress the importance of building a diversified effort that is critically reviewed at every step--particularly during the early stages.

Similar thinking dictates that major DNA sequencing efforts be phased in gradually, with each increment awaiting expected improvements in technology and careful evaluation of their impact on costs before projects ascend to the next level in volume and complexity. Committee members feel that breakthroughs in technology must come before there is any concerted move to a massive "assembly-line" approach to DNA sequencing. Indeed, the need for a centralized effort in DNA sequencing conceivably may never arise if appropriate technological developments in automation enable a fully decentralized approach. However, some consolidation of efforts is expected as improvements in technology dictate. Despite the realization that better approaches to DNA sequencing are needed, however, there also is a need to develop them in the context of sequencing biologically relevant segments of DNA. Moreover, decisions to proceed will involve a constant interplay of costs and value considerations.

The current limitations on technology for mapping genes are different than those faced for sequencing DNA. Genetic mapping now can go ahead on a substantial scale. The Committee recognizes that the available technology is ready for construction of a 1-centiMorgan average resolution linkage map, and the pace of this effort will depend primarily on available funding--not on an awaited technology. Although significant improvements are to be actively sought, physical mapping can now be done on a substantial scale with a fairly centralized effort. Directed projects to develop such maps are expected to spur developments in technology.

Specific recommendations and needs for mapping and DNA sequencing include the following:

- Three types of maps should be developed in parallel, beginning immediately (high resolution genetic maps, macrorestriction maps, and linked libraries).
- Support is needed for the following smaller-scale efforts to improve mapping and DNA handling technologies:
 - Physical means for separating intact human chromosomes or other large DNA fragments with high resolution;
 - Isolating and maintaining human chromosome fragments within cultured cell lines;
 - Cloning and purifying large DNA fragments;

- Ordering adjacent DNA fragments in a DNA clone bank; and
- Automating DNA mapping, including DNA purification and hybridization analysis, handling of DNA samples, and mathematical analysis to aid in map construction.
- Full-scale DNA sequencing should not begin until technology developments dictate greater efficiency of effort. To achieve that goal, a gradual build-up through practical sequencing undertakings will be helpful, particularly as they provide increased confidence in the scientific value of the data being obtained. Thus, contiguous megabase sequencing on model systems (such as the major histocompatibility locus) could begin in 1 to 2 years, building to sequencing of small human chromosomes within 5 years. The full human genome might be tackled during years 10 to 15.
- Great emphasis must be placed on technology development and its dependence on interdisciplinary efforts. Even modest improvements in slow ("rate-limiting") steps in sequencing can bring about significant gains in efficiency.
- Cooperation between industrial, academic, and Federal laboratories also must be expressly encouraged. The successful transfer of new technologies is one of the most important achievements expected from this program. For example, new instruments most certainly will be developed as an outgrowth of this effort.
- The Ad Hoc Program Advisory Committee carefully discussed the important role of genetic model systems in complementing efforts to better understand the human genome. In different phases of this project, various nonhuman model systems will provide valuable insights in establishing techniques and providing crucial comparative landmarks in this uncharted territory. Sound scientific proposals that focus on model systems--including *Drosophila*, the mouse, or even simple plant systems--may well provide unique insights into technical problems and could also lead to solving problems directly related to human disease. A continuing effort will be needed to coordinate efforts with other established biomedical research programs to avoid unnecessary overlap.
- Consideration should be given to supporting some projects to explore the feasibility of constructing cDNA maps. The Committee recognizes the many challenges involved in undertaking such projects, particularly in deciding what types of cells should be used for source materials and in obtaining low abundance molecules of messenger RNA. Also, it is not yet known to what extent eukaryotic cells rely on control at the transcriptional level. Nonetheless, some exploratory efforts could uncover highly valuable information about cellular functions.

Information and Biological Materials

The Human Genome Program poses major new challenges in the handling, storage, and analysis of biological materials and information. Special resources will be needed for dealing with materials, and new methods must be developed to improve the efficiency with which materials are exchanged among research groups. Similarly, the program will generate vast amounts of data, and they also must be stored, handled, and analyzed efficiently.

Special provisions must be made for collecting genetic materials from families in which genetic diseases segregate. The coordination of this effort also very quickly takes on information handling challenges. Moreover, it tends to involve existing research activities outside the new program. Such questions of overlap help prompt the need for a subcommittee to deal specifically with oversight of information resources. Key needs for dealing with information and biological materials include the following:

- Biological resources collections are vital for distributing valuable biological materials and preserving them in archives. For the program, central, federally supported repositories are crucial for two categories of materials: cells and cloned DNA segments and probes.
- The familial cell lines needed to construct a 1-centimorgan average resolution map are already available as cell lines kept in a repository in Paris. However, a more conveniently accessible repository for such cell lines should perhaps also be established in the United States.
- The collection of genetic materials from families in which genetic diseases segregate is largely underfunded. Efforts to collect such materials badly need better coordination. However, the central collection effort may not itself be a part of the genome project, and other institutes of NIH must be called upon to deal with collections needed for studying particular diseases, such as schizophrenia and heart disease.
- Cloned DNA segments are a vital but, currently, very costly item to collect, analyze, and store. Pilot projects must be undertaken to solve technical and cost problems.
- A national center will be required for coordination and reasonably uniform integration of the many data bases that the genome project will generate. The National Library of Medicine may be the right place for establishing such a national center. Conceivably, the current Biotechnology Information Center could grow into this role.
- Coordination of data bases is an absolute requirement. A community minimum standard should be established for all NIH-sponsored data bases that would allow format and database management system inter-convertibility and maximum ease of cross-indexing. The existing and needed data bases, not to be limited to those containing information on human genetics, should include:

- DNA sequences, protein sequences;
- Genetic linkage maps (restriction fragment length polymorphisms);
- Physical maps of overlapping clones and of restriction sites;
- Cytogenetic maps;
- Tracking materials generated by the program;
- Data bases such as the Brookhaven Crystallographic Data Base;
- Bibliographic references relevant to data generated;
- Full-text data bases, such as Mendelian Inheritance in Man;
- Secondly derived data bases of patterns, such as those consisting of patterns defining protein or DNA functional features; and
- Genetic markers and data bases of genes, such as the Yale-Howard Hughes data base.

- The proposed national genome information coordinating center will have as one of its charges taking basic research in informatics and applying it to existing data bases that represent national research resources. Having a national center in which all available data bases are maintained and made accessible makes possible other local centers that will be free to explore different approaches and uses.
- Distribution of and free access to the data bases must be fully encouraged. Thus, the data must be in the public domain, and the redistribution of the data should remain free of royalties. Moreover, the operation (collection and organization) of the human genome databases should not be linked to income from its distribution. All data coming from federally funded research related to the Human Genome Research Program should be expeditiously submitted and entered into national databases.
- Basic research needs in information include research to improve data representation, man-machine interfacing, investigations into new chips and new architecture, and developing new means for examining genomic variation and three-dimensional structure, finding similarities, recognizing sites and features, and analyzing mapping strategies. It should be done at the proposed center and extramurally, and it should feed back into the data bases.

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Sheraton International Conference Center
Reston, Virginia

February 29-March 1, 1988

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Sheraton International Conference Center
Reston, Virginia

February 29-March 1, 1988

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AD HOC PROGRAM ADVISORY COMMITTEE ON COMPLEX GENOMES

Sheraton International Conference Center
Reston, Virginia

February 29-March 1, 1988

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National Research Council
Commission on Life Sciences
Board on Basic Biology
Committee on Mapping and Sequencing the Human Genome*

RECOMMENDATIONS

Mapping

- Full-scale mapping (not gene by gene), both genetic linkage and physical, should begin immediately.
- "Because the technology needed for genetic linkage mapping with RFLPs is more advanced than that for physical mapping, an immediate emphasis should be placed on completing the genetic linkage map. A project with the goal of attaining of a fully connected map with an average resolution of 1 cM is strongly recommended."
- All types of maps (restriction-site maps, cDNA maps, ordered DNA clone maps, and genetic linkage maps) "need to be coordinated as part of a human genome project."
- Encourage researchers' natural tendency to construct detailed maps of chromosomal regions of particular interest.
- "The committee specifically recommends against a centrally imposed plan to proceed from lower to higher resolution as is implicit, for example, in proposals to complete the entire physical map before initiating pilot sequencing projects."
- "Most support should be to groups that are attempting to map large genomes, with support for different mapping methods proceeding in parallel."
- Development and refinement of techniques should be emphasized early in the mapping part of the project.
- Improved methods for the following would facilitate map construction and usefulness:
 - Physically separating intact human chromosomes;
 - Isolating and immortalizing identified fragments of human chromosomes in cultured cell lines;
 - Cloning cDNA from low abundance mRNA and obtaining "normalized" cDNA libraries;
 - Cloning and purifying large DNA fragments;

- Separating large DNA fragments with higher resolution;
- Ordering the adjacent DNA fragments in a DNA clone bank, including mathematical and statistical work that would aid in map construction;
- Automating DNA mapping, including DNA purification and hybridization analysis, and handling of many DNA samples simultaneously; and
- Data recording, storage, and analysis.

Sequencing

- "Initially, improvements in existing technology and the development of new technology directed toward the long-range goal of a complete human genome sequence should be vigorously encouraged. This effort would include applications of automation and robotics at all steps in cloning and sequencing." "The awarding of competitive grants to individuals and to larger groups organized into cooperative, multidisciplinary centers is viewed by the committee as the most effective way to achieve these goals."
- "The disparities between the capabilities of current technology and the magnitude of the work required to sequence the human genome suggests that fundamentally different technologies deserve serious exploration."
- "Human gene sequencing by individual research groups interested in specific genes should be strongly supported by standard research grants."
- Encourage development of technology to extend the length of contiguous sequence that can be determined on a single polyacrylamide gel.
- A pilot study to be "initiated immediately would define as its goal sequencing approximately 1 million nucleotides of continuous sequence."
- A mechanism of quality control must be developed to monitor the groups that are contributing extensive sequence DNA information. One might consider an external group that functions as the National Bureau of Standards does to provide independent quality control.

Biological Material

- Ordered DNA clone collections should be completed. "A facility for collecting and distributing material should be organized to handle the cloned DNA fragments generated and mapped in the many different laboratories involved." This facility would store the appropriate clones, index them according to plan, and then redistribute them upon request.
- Stability of stored DNA fragments is still a problem.
- There may be a need for more than one production center (in addition to CEPH) to grow cells and to produce and distribute DNA.

Information Handling

- All human map data should be accessible from a single data base.
- "To derive the full benefit of the human genome sequence will require many new tools, including a comprehensive data base of DNA sequences from other organisms."
- A centralized facility is needed to collect, store, analyze, and distribute information.
 - An initial analysis of these data should be carried out in the facility;
 - All data must be provided to the center in electronic or magnetic form; and
 - The information center must be linked to data users via a computer network.
- "Decisions for a major push on bulk sequence data collection, as distinct from the envisioned pilot projects that push technology development, would depend on how fast the new sequencing technologies develop."
- Encourage the activities of those individuals who combine skills in computer programming and biology as they will be needed to generate the DNA sequence search routines of greatest utility to the biological community.

Implementation

- Funding ought not to be provided at the expense of currently funded biological research.
- Funding ought to be distributed by peer review, grants to be awarded for 3- to 7-year periods. The committee specifically recommends the form of peer review in place at NIH.
- "Establishment of a competitive grant program specifically focused on improving in 5- to 10-fold increments the scale or efficiency of mapping and sequencing the human genome. These grants would be designed to support work that is more technologically oriented than most ongoing biological research."
- "This project ought to include work by both small research laboratories and larger multidisciplinary centers formed by juxtaposing several small research groups having different expertise."
- "Multidisciplinary centers would comprise 3 to 10 research groups, each with an outstanding independent scientific director and a different but related focus. The center could share equipment and personnel as a core facility."

• The committee is not in favor of establishing a few large production centers for mapping and sequencing, given the current state of technology.

- Support for some centers and pilot projects may be amenable to the contract funding mechanism awarded on a competitive basis.
- Competition between centers should be encouraged.
- Include selected other organisms required for interpretation of the human genome map and sequence.

Management Strategies

- "It is imperative to design a management system that will provide oversight, coordination, review of progress, and forward planning."
- The committee reached a consensus for a lead agency, either NIH or DOE.
- "Although the lead agency would have the ultimate responsibility for funding and policy decisions, it would draw on the advice and expertise of a Scientific Advisory Board." Responsibilities of the Board would be to:
 - Facilitate coordination;
 - Assure accessibility of information and materials;
 - Monitor quality of research by helping to assure a uniform standard of peer review;
 - Suggest mechanisms for quality control on mapping and sequence data;
 - Promote international cooperation;
 - Make recommendations concerning the establishment of large sequencing endeavors; and
 - Publish periodic reports on progress, problems, and research recommendations.
- The Scientific Advisory Board would require funding, perhaps from private institutions as well as the lead agency."
- If funding is provided by several separate U.S. government agencies, as well as by private funds, an effective reviewing body will be needed to avoid excessive duplication of effort and to oversee cooperation between research groups.
- The committee believes it will become necessary to have some major organized mechanism for international cooperation. The objective would be to collate data and ensure rapid accessibility to it, and to distribute materials, such as cloned DNA fragments.

Funding Projection

- Estimated cost: \$200 million per year, to be reached during the third year of the project.
- Estimate is based on a projected total of 1,200 individuals & \$160,000 annually.
- "The committee's possible scenario divides the project into 3 five year periods. During each period, mapping and sequencing efforts five times as complex as the next lower numerical designation would be undertaken at constant cost, reflecting five fold increments in technological sophistication. This plan requires the following:
 - A major effort must be expended in technological development;
 - "New methods of DNA subcloning and processing will have to be developed (or present ones automated) to stay within the estimated costs;
 - DNA clones from an ordered DNA clone collection will be sequenced, thereby producing large contiguous stretches of DNA sequence that are immediately useful;
 - This effort will require the recruitment of scientists with extensive experience in mapping and sequencing. The multidisciplinary centers supported by the project will play a key role in training new independent scientists--a major benefit to the biological community.

COST APPENDIX DEVELOPED BY
THE AD HOC PROGRAM ADVISORY COMMITTEE ON COMPLEX GENOMES

Mapping Working Group

- Construction of a genetic map with an average 1-centiMorgan resolution should proceed as rapidly as possible. It will cost \$10 to \$15 million per year for 3 to 5 years, for a total of \$30 to \$50 million. Work on nonhuman model systems should also be planned at an additional total cost of \$4 million per year, or \$20 million for 5 years.
- Physical mapping of chromosomes also should be undertaken with particular attention paid to improving technologies. Funding should support 10 large and varied projects, such as mapping the *Drosophila* genome or a small human chromosome, each costing \$1 million per year for 3 to 5 years. Once completed, such advances set the stage for mapping human chromosomes during the next 5 to 10 years.
- Targeted technology development that is not incorporated into specific mapping projects during the first 3- to 5-year period will cost \$5 million per year, for a total of \$15 to \$25 million.

DNA Sequencing Working Group

- The principal short-term goal is to establish 10 to 20 exploratory research programs of varied size, with a substantial component in technology development. At the outset of a 5-year period, spending will be \$7 million per year, growing to \$60 million per year.
- Technology changes could dramatically affect this component of the overall effort, so that in the second 5-year period, complete sequencing of small-sized human chromosomes will be undertaken, leading to an effort on the entire genome between years 10 and 15.

Information Working Group

- A high priority is to establish a national information coordinating center. Starting from an initial outlay of \$3 million per year, the budget for the center should grow to \$8 to \$9 million per year after 3

[These figures are based on: 30 to 35 FTEs at the steady state at a cost of \$3 to \$3.5 million); \$2.5 million per year in computational resources; and \$2.5 million per year in targeted extramural support.]

- Information research through a grants program: An additional ten 3-year grants (with an average size \$300,000 to \$500,000) should be funded the first year, building to a total of 30 such grants running per year after 5 years. The annual budget would grow from about \$3 to \$6 million to about \$12 million.
- In addition to support for existing national data bases, 10 to 15 percent of total costs of mapping and sequencing projects should be added on for the purpose of data organization.
- Centers of excellence devoted to information analysis should be established either within institutions already conducting mapping and sequencing projects or at universities without such activities but with more general interests in related areas, such as protein structure analysis or genetics. Core facilities and central research support will require \$1 million per year for each center. Thus initially, two to three will cost \$3 million per year, growing after 5 years to about 10 with an aggregate total budget of \$10 million.

Biological Materials Working Group

- The cost for developing and maintaining a full collection of overlapping cosmids of the human genome could amount to \$100 million, based on current estimates of \$10 million per year for 10 years. However, technological developments are expected to reduce this budget significantly, possibly by an order of magnitude.
- Before any undertaking to build a full collection begins, pilot projects to improve technology are needed, and they should be funded through competing grants totalling \$1 to \$2 million per year.
- The estimated expense for setting up a U.S. repository for familial cell lines to construct reference maps is \$1 to \$2 million per year for a 5-year period, or a total cost of \$5 to \$10 million.
- Some 20 to 25 regional human genetics centers, each employing one to two experts, should be established at an aggregate annual cost of \$2 to \$3 million for 10 years. In addition, the Camden, N.J. repository should be budgeted for \$1 million per year for 10 years. Total Cost: \$20 to \$40 million.
- Costs could amount to \$5 million (total) over 5 years for hybrid cell lines containing a full collection of human chromosomes with necessary replicates.
- As an approximation dependent on unrealized (not yet undertaken) improvements in technology, the working group calculates that introduction of 10,000 cosmids per year into a repository requires an annual budget of \$10 million, for a projected cost of \$50 million for 5 years.

- Research and development for competitive grants exploring methods for more cost-effective cosmid acquisition, verification, and storage: \$1 to \$2 million per year, to begin immediately.
- About 4,000 RFLPs are needed to develop a map having a 1-centiMorgan resolution. The anticipated cost is \$1 million per year for 5 years, for a total of \$5 million.

Estimated Costs for Training Needs

- The program should be training 50 predoctoral students and recruiting 50 postdoctoral scientists--building over a 5-year period to 150 predoctoral and 150 postdoctoral researchers per year. Computing annual training costs at \$20 thousand and \$25 thousand per individual, respectively, the training program will grow from \$2 million to \$7 million per year in 5 years.
- Information handling will require a special component for training in biology and computer/mathematical analysis:
 - Initially it should support three to five such programs with three to five students each, at an initial program cost of \$700,000 per year, building to 50 to 75 students per year after 5 years with an annual program cost of about \$7.5 million
 - Training must extend to postdoctoral level scientists and senior visiting scientists, with the annual program initially set at \$1 million for about 20 postdocs and five visiting scientists but growing after 5 years to 50 postdocs and 10 visiting scientists for a total annual cost of about \$6 million.
 - Training of general molecular biologists in computational methods of genomic analysis, including the development of curricula and educational materials, with the expectation that all molecular biology graduate students should eventually take one such course. Cost: \$750,000 per year.

Construction and Infrastructure Costs

- For building and remodeling laboratory facilities, particularly as efforts are begun to conduct large-scale DNA sequencing at the megabase level and beyond, an overall budget of \$30 million is recommended (alternatively, an appropriate estimate of this figure is 20 percent of the total budget), with outlays of about \$3 million beginning in the second year and the remainder to be spent over the next several years.

Provision must be made for administrative costs incurred because of the new

TECHNOLOGY DEVELOPMENT, MAPPING, AND DNA SEQUENCING IN SUPPORT OF THE HUMAN
GENOME PROGRAM

P. P. 141 K.W. 1415010, 0755045, 1002058, 1004017, 1003012, 1012038, 0710030

Office of Human Genome Research

This Program Announcement restates the interest of the National Institutes of Health (NIH) in receiving research grant applications for studies related to the Human Genome Initiative. The present announcement supersedes the previous NIH-wide Program Announcement (November 4, 1988) on mapping and determining the DNA sequences of the genomes of the human or of model organisms. The objective is to stimulate creative, innovative research that will substantially improve the capacity, efficiency and accuracy with which mapping and DNA sequence data can be obtained, analyzed, and distributed.

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BACKGROUND INFORMATION

The NIH is currently engaged, along with several other federal, private, and international organizations, in a research program known as the Human Genome Initiative. This program is designed to characterize the human genome and the genomes of selected model organisms. It has several interrelated goals: the construction of high resolution genetic linkage maps; the development of a variety of physical maps; the determination of the complete nucleotide sequence of the DNA of selected organisms; the development of the capability for collecting, storing, distributing, and analyzing the data and materials produced; and the development of appropriate new technologies necessary to achieve these objectives. The information that will be obtained within the genome project will be a resource for studies of gene structure and function and will promote research into the genetic aspects of human disease. In this way, the Human Genome Initiative will serve as an underlying source of information for, and stimulus to, a wide range of studies from the most basic to targeted and clinical programs across the spectrum of NIH interests and responsibilities.

In the past two years, several announcements/solicitations for grant applications related to the Human Genome Initiative have been published in the NIH Guide for Grants and Contracts. These include two broad program announcements and several Requests for Applications. This Program Announcement consolidates the prior announcements/solicitations in one document and emphasizes the continuing, ongoing interest on the part of the NIH in receiving grant applications for support of research projects that address the goals of the genome program with a wide range of research activities. One area in which research activities are encouraged is the development of improved technology for physical mapping, for the determination of DNA sequences, and for the management of the information that accrues. A separate, but equally important, area includes research projects that seek to increase the information available about specific genomic regions through the expansion of genetic maps, the construction of physical maps, or pilot projects for large-scale DNA sequence determination.

Creative, novel approaches in all these areas will be essential to the success of the genome project. To this end, the NIH encourages interdisciplinary programs that draw from fields such as information science, chemistry, physics, and engineering, in addition to the biological sciences.

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TECHNOLOGY DEVELOPMENT, MAPPING, AND DNA SEQUENCING IN SUPPORT OF THE HUMAN
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P.T. 34; K.R. 1215010, 0755045, 1002058, 1004017, 1003012, 1002048, 0710030
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SACRAMENTO INFORMATION

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Grants & Contracts

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TECHNOLOGY DEVELOPMENT, MAPPING, AND DNA SEQUENCING IN SUPPORT OF THE HUMAN
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P.O. Box 34, Rm. 1215018, 0755045, 1002058, 1004017, 1003012, 1002008, 0710030
OFFICE OF HUMAN GENOME RESEARCH

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Creative, novel approaches in all these areas will be essential to the success of the genome project. To this end, the NIH encourages interdisciplinary programs that draw from fields such as immunology, chemistry, physics, and engineering, in addition to biology.

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361. Progress will be accelerated by cooperation and interaction among
362. investigators. Therefore, it is expected that all materials and information
363. derived from this work will be made available to the scientific community in a
364. timely manner, in accord with Public Health Service policy. Within the genome
365. program, awardees will be expected to share information and to work closely
366. with other laboratories involved in related projects.

367. RESEARCH SCOPE

368. This Program Announcement is intended to emphasize the ongoing commitment of
369. the NIH to the specific goals of the genome project and to the development of
370. methodological tools and resources which would support this effort, including
371. the storage and retrieval of materials and data. Applications responsive to
372. this announcement will include a broad spectrum of research approaches to
373. genetic and physical mapping, DNA sequencing, data handling and new methods of
374. data interpretation. Development of new and imaginative technologies needed
375. to support the genome project are especially encouraged. The topics described
376. below are not intended to limit the types of applications that are acceptable
377. in response to this announcement, but rather to illustrate the range of work
378. that will be needed to attain the goals of the genome project.

379. However, research directed toward analysis of the biological function of
380. specific genes or gene systems, or the application of genetic information to
381. the understanding, diagnosis, prevention, or treatment of specific genetic
382. disorders is not within the scope of the genome program. Such work is
383. currently supported by a number of other programs at the NIH. Information
384. about these programs can be obtained from individual Institutes. Potential
385. applicants are encouraged to contact one of the representatives listed below
386. to discuss the proposed research project and for additional information.

387. Technology Development

388. The objective is to stimulate creative, innovative research that will lead to
389. substantial improvements in the speed, efficiency and accuracy with which
390. mapping and DNA sequence data can be obtained, analyzed, and distributed.
391. Such improvements can be achieved through automation of existing methodology,
392. development of new approaches, or both. Multi-disciplinary approaches to the

393. Vol. 18, No. 26, July 28, 1989 - Page 4
394. attainment of these goals are encouraged. Examples of the problems for which
395. improved technological solutions and/or automation are needed are:

- 396. o generating, purifying, and cloning large DNA fragments;
- 397. o constructing physical maps, including long-range restriction maps
398. and overlapping sets (contigs) of DNA fragments that are derived
399. from specific chromosomal regions and are connected into more
400. extensive physical arrays;
- 401. o determining relationships between genetic and physical maps;
- 402. o locating specific genes on genetic and physical maps and within
403. regions of sequenced DNA;
- 404. o determining DNA sequence, including assembling overlapping DNA
405. sequences into longer arrays;
- 406. o storing, analyzing, and distributing the data obtained in each of
407. these activities; and

- 408. o storing and distributing the materials generated by all of these
409. activities.

410. Applicants are advised to take several general considerations into account
411. when designing new projects.

- 412. o Methodological improvements have played an important role in
413. advancing biological research, never more so than in the past
414. twenty years. In general, when technology development has been
415. successful, it has been driven by the desire to solve specific
416. scientific problems. Therefore, it is reasonable to expect that,
417. within the context of the genome program also, the most successful
418. new technologies will come from those endeavors in which the
419. attempt to develop better technology occurs in the

417. sequences in longer arrays,
418. o storing, analyzing, and distributing the data obtained in each of
419. these activities; and
420.

421. o storing and distributing the materials generated by all of these
422. activities.
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428. advancing biological research, never more so than in the past
429. twenty years. In general, when technology development has been
430. successful, it has been driven by the desire to solve specific
431. scientific problems. Therefore, it is reasonable to expect that,
432. within the context of the genome program also, the most successful
433. new technologies will come from those endeavors in which the
434. attempt to develop better technology occurs in the context of a
435. specific research problem related to genomic analysis. Applicants
436. are encouraged to clearly define the biological problem for which
437. the technological solution is being devised. Applicants whose
438. expertise is primarily non-biological and who are interested in
439. addressing problems of genome analysis with new, non-biological
440. tools are especially encouraged to interact closely with
441. biologists.
442.

443. o It has been suggested that to significantly increase the rate at
444. which mapping and sequence data can be acquired, efforts should be
445. directed toward improving by three- to five-fold the scale and/or
446. efficiency with which particular steps in mapping, sequence
447. determination, or data analysis can be accomplished. Such an
448. incremental increase can serve as a useful benchmark in designing a
449. research program.
450.

451. o Achievement of such a significant improvement in analytical
452. capability may require entirely new approaches. Methods that have
453. been useful for addressing particular needs in the past, such as
454. determining the sequence of a few kilobases of DNA, may not be
455. adequate for addressing comparable problems on a much larger scale.
456. The NIH recognizes that novel approaches may involve a considerable
457. degree of risk and encourages submission of high-risk, high pay-off
458. projects in response to this announcement.
459.

460. Mapping and DNA Sequencing

461. The objective is to increase our knowledge of the genetic and physical maps
462. and the DNA sequence of selected organisms, leading up to the complete maps of
463. the human genome and the complete human DNA sequence. Research projects in
464. the following areas are encouraged:
465.

466. o expanding the genetic map of the human, or of those model organisms
467. for which such information would serve to promote the objectives of
468. the overall genome program;
469.
470. o constructing physical maps of the chromosomes of the human and of
471. model organisms, including projects for large-scale physical
472. mapping; and
473.
474. o pilot projects for large-scale DNA sequence determination,
475. involving the DNA of model organisms or regions of the human
476. genome.
477.
478.

The primary goal of research projects proposed under this section will be the generation of a substantial amount of new mapping and/or sequence information. The project may utilize current technology or propose new or improved technology. If current technology is used, it should be used at or near its limits in order to explore its capabilities.

Because of the extensive amount of information already available about the genetics and molecular biology of *E. coli*, *S. cerevisiae*, *D. melanogaster*, *C. elegans*, and *M. musculus*, the genome program is particularly interested in promoting study of these models. However, research projects that involve other models are also expected to make important contributions to the Human Genome Initiative by means of both development of new technology and improved understanding of genome structure through comparative studies. Thus, no model organism is excluded from the genome program a priori. However, applicants proposing to study models other than those named above must provide a rationale, in terms of the goals of the overall genome program, for the use of such another model.

MECHANISMS OF SUPPORT

Support for this program will be through research grants, including project grants (R01), program project grants (P01), FIRST awards (R29), resources related research projects and biotechnology resource grants (R24, P41), Research Career Development Awards (R04), conference grants (R24, P41), Business Innovation Research (SBIR) grants (R43, R44). Because not all institutes support all of the above mechanisms, potential applicants are encouraged to contact the representatives listed below for additional information. Policies that govern research grant programs of the NIH apply to this program. Consortium arrangements and collaborative projects among scientists with skills in biological sciences, chemistry, physics, information science, and engineering are encouraged.

APPLICATION AND REVIEW PROCEDURES

Applications in response to this announcement will be reviewed in accordance with the usual NIH peer review procedures. They will first be reviewed for scientific and technical merit by a special study section in the Division of Research Grants organized for this purpose. Following the initial review, the applications will be considered by the appropriate National Advisory Board or Council. Review criteria that will be used to assess the scientific merit of an application are the following:

- o Scientific merit;
- o Potential value of the research for furthering the goals of the genome project;
- o Feasibility of the research and adequacy of the experimental design;
- o Significance and originality of the research and methodological approaches, as they relate to the genome project;
- o Training, experience, research competence, and dedication of the investigator(s);
- o Adequacy of available facilities;
- o Provisions for the protection of human subjects, the humane care of animals, and biosafety conditions;

- o Appropriateness of the requested budget for the work proposed.

Because the significance of the proposed research project to the goals of the Human Genome Initiative is a criterion for review, consultants must consider this aspect in the evaluation of an application submitted in response to this Program Announcement. Applicants are, therefore, encouraged to consult with one of the staff listed below before submission, to discuss the relevance of a proposed application to the genome program.

METHOD OF APPLYING

Applications should be submitted on form PHS 398 (rev. 11-80) Application kits are available in most institutional libraries. For more information, contact the Grants Information Service.

481. The primary goal of research projects proposed under this section will be the
482. generation of a substantial amount of new mapping and/or sequence information.
483. The project may utilize current technology or propose new or improved
484. technology. If current technology is used, it should be used at or near its
485. limits in order to explore its capabilities.

486. Because of the extensive amount of information already available about the
487. genetics and molecular biology of *E. coli*, *S. cerevisiae*, *D. melanogaster*, *C.*
488. *elegans*, and *M. musculus*, the genome program is particularly interested in
489. promoting study of these models. However, research projects that involve
490. other models are also expected to make important contributions to the Human
491. Genome Initiative by means of both development of new technology and improved
492. understanding of genome structure through comparative studies. Thus, no model
493. organism is excluded from the genome program a priori. However, applicants
494. proposing to study models other than those named above must provide a
495. rationale, in terms of the goals of the overall genome program, for the use of
496. such another model.

497. MECHANISMS OF SUPPORT

498. Support for this program will be through research grants, including project
499. grants (R01), program project grants (P01), FIRST awards (R29), resources
500. related research projects and biotechnology resource grants (R24, P41),
501. Research Career Development Awards (K04), conference grants (R13) and Small
502. Business Innovation Research (SBIR) grants (R43, R44). Because not all
503. institutes support all of the above mechanisms, potential applicants are
504. encouraged to contact the representatives listed below for additional
505. information. Policies that govern research grant programs of the NIH apply to
506. this program. Consortium arrangements and collaborative projects among
507. scientists with skills in biological sciences, chemistry, physics, information
508. science, and engineering are encouraged.

509. APPLICATION AND REVIEW PROCEDURES

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511. with the usual NIH peer review procedures. They will first be reviewed for
512. scientific and technical merit by a special study section in the Division of
513. Research Grants organized for this purpose. Following the initial review, the
514. applications will be considered by the appropriate National Advisory Board or
515. Council. Review criteria that will be used to assess the scientific merit of
516. an application are the following:

- 517. o Scientific merit;
- 518. o Potential value of the research for furthering the goals of the
519. genome project;
- 520. o Feasibility of the research and adequacy of the experimental
521. design;
- 522. o Significance and originality of the research and methodological
523. approaches, as they relate to the genome project;
- 524. o Training, experience, research competence, and dedication of the
525. investigator(s);
- 526. o Adequacy of available facilities;
- 527. o Provisions for the protection of human subjects, the humane care of
528. animals, and biosafety conditions;

- 529. o Appropriateness of the requested budget for the work proposed.

530. Because the significance of the proposed research project to the goals of the
531. Human Genome Initiative is a criterion for review, consultants must consider
532. this aspect in the evaluation of an application submitted in response to this
533. Program Announcement. Applicants are, therefore, encouraged to consult with
534. one of the staff listed below before submission, to discuss the relevance of a
535. proposed application to the genome program.

536. METHOD OF APPLYING

537. Applications should be submitted on Form PHS 398 (Rev. 10-1-80). Application
538. kits are available in most areas.

- o Adequacy of available facilities;
- o Provisions for the protection of human subjects, the humane care of animals, and biosafety conditions;

- o Appropriateness of the requested budget for the work proposed.

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METHOD OF APPLYING

Applications should be submitted on Form PHS 398 (rev. 10/88). Application kits are available in most institutional business offices and from the Office of Grants Inquiries, Division of Research Grants, Westwood Building, Room 449, National Institutes of Health, Bethesda, Maryland 20892; telephone (301) 496-7441.

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Applications will be accepted in accordance with the usual NIH receipt dates that apply for the various mechanisms listed under MECHANISMS OF SUPPORT. It is essential that applicants type "Technology Development, Mapping, and DNA Sequence Determination in Support of the Human Genome Initiative" in item 2 on the face page of the application form. The original and six copies of the application should be submitted to the following office:

Application Receipt Office
Division of Research Grants
Westwood Building, Room 240
National Institutes of Health
Bethesda, Maryland 20892**
Telephone: (301) 496-7273

The conventional presentation for grant applications should be utilized.

Funding decisions will be based on recommendations of the initial review group and of the National Advisory Council regarding scientific merit and program relevance, as well as on the availability of funds.

INQUIRES

It is strongly recommended, but not required, that potential applicants contact the Office of Human Genome Research (OHGR) or the staff member at the appropriate NIH institute to discuss research objectives.

BID	CONTACT	BUILDING	ROOM	TELEPHONE
OHGR	Bettie Graham, Ph.D.	Shannon	201	496-0844
NIDDK	Robert Katz, Ph.D.	Westwood	507	496-7997
NCI	Cheryl Marks, Ph.D.	Executive Plaza South	630	496-7028
FIC	Lynn Amende, Ph.D.	38A	613	496-6688
DDR	Charles Coulter, Ph.D.	Westwood	8A11	496-5411
NIA	Huber R. Warner, Ph.D.	31	5B39	496-6402
NICHD	Delbert Dayton, M.D.	Executive Plaza North	5C19	496-5541
NINDS	N.C. Myrianthopoulos, Ph.D.	Federal	8C04	496-5821
NEM	Arthur Broering, Ph.D.	38A	8C16	496-4621
NIDR	John Townsley, Ph.D.	Westwood	506	496-7807

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NLM	Arthur Broering, Ph.D.	38A	8C16	496-4621
NIDR	John Townsley, Ph.D.	Westwood	506	496-7807

601.	NIGMS	Irene Eckstrand, Ph.D.	Westwood	920	
602.	NIAMS	Steven Hausman, Ph.D.	Westwood	403	496-7137
603.	NHLBI	Carol Letendre, Ph.D.	Federal	506	496-7495
604.	NIAID	William Duncan, Ph.D.	Westwood	754	496-6402
605.	NEI	Jack McLaughlin, Ph.D.	31	6A08	496-5598
606.					496-9110

607. Mailing address for the above offices: Bethesda, Maryland 20892
608. All Bethesda telephone numbers are in area code 301.

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611. **THE MAILING ADDRESS GIVEN FOR SENDING APPLICATIONS TO THE DIVISION OF
612. RESEARCH GRANTS OR CONTACTING PROGRAM STAFF IN THE WESTWOOD BUILDING IS THE
613. CENTRAL MAILING ADDRESS FOR THE NATIONAL INSTITUTES OF HEALTH. APPLICANTS WHO
614. USE EXPRESS MAIL OR A COURIER SERVICE ARE ADVISED TO FOLLOW THE CARRIER'S
615. REQUIREMENTS FOR SHOWING A STREET ADDRESS. THE ADDRESS FOR THE WESTWOOD
616. BUILDING IS:

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618. 5333 Westbard Avenue
619. Bethesda, Maryland 20816
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